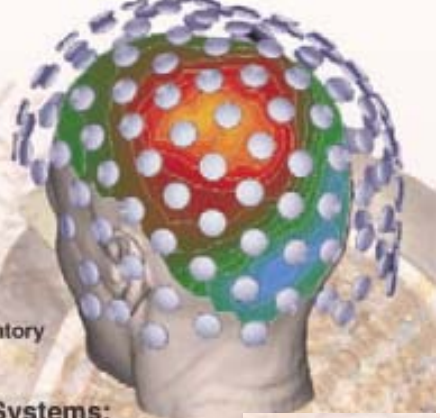
Frontiers in Science



Public Lecture Series
Sponsored by the Fellows of Los Alamos National Laboratory

Measuring Small Magnetic Fields in Living Systems: From Understanding the Brain to Cancer Detection

Dr. Michelle A. Espy, Biophysics Group

Española: Wednesday, 2 October 2002, at 7:30 PM
Center for the Arts Theater, Northern New Mexico Community College

Santa Fe: Wednesday, 9 October 2002, at 7:30 PM
James A. Little Theater, New Mexico School for the Deaf

Los Alamos: Thursday, 10 October 2002, at 7:30 PM
Duane W. Smith Auditorium, Los Alamos High School

Taos: Wednesday, 16 October 2002, at 7:30 PM
Taos Convention Center

The Complexity, Simplicity, and Unity of Living Systems

Dr. Geoffrey B. West, Elementary Particle and Field Theory Group

Santa Fe: Wednesday, 13 November 2002, at 7:30 PM
James A. Little Theater, New Mexico School for the Deaf

Taos: Thursday, 14 November 2002, at 7:30 PM
Taos Convention Center

Española: Wednesday, 20 November 2002, at 7:30 PM
Center for the Arts Theater,
Northern New Mexico Community College

Los Alamos: Thursday, 21 November 2002, at 7:30 PM
Duane W. Smith Auditorium, Los Alamos High School

Admission Is Free

http://stb.lanl.gov/fellows/fellows.html

Los Alamos
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NNSA Los Alamos

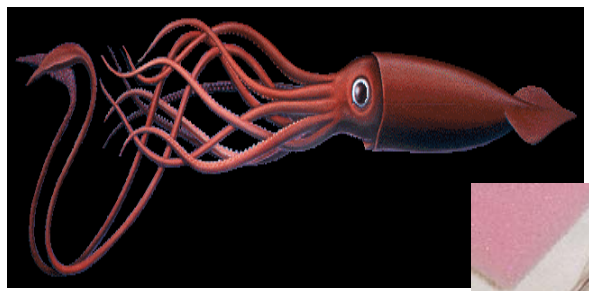
Physics

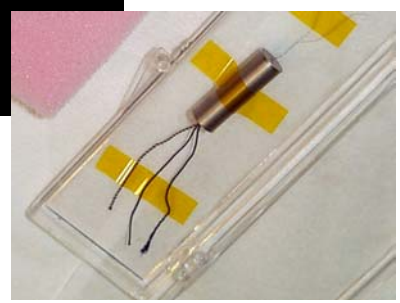
Measuring Small Magnetic Fields in Living Systems: from Understanding the Brain to Cancer Detection.

Michelle Espy
SQUID Team

Biophysics Group, P-21

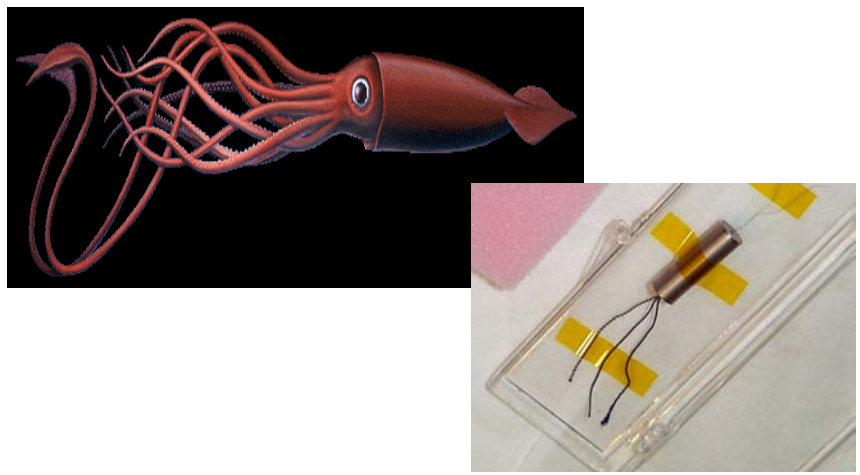
Los Alamos National Laboratory





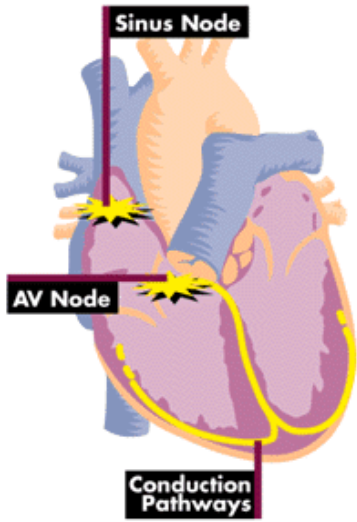
The Superconducting Quantum Interference Device (SQUID) is the world's most sensitive detector of magnetic fields.

This talk is about how SQUIDs are used to measure the tiny magnetic fields associated with the processes of life in health and illness.



Your body is electric, and thus magnetic

Neuron in the human brain



Human heart

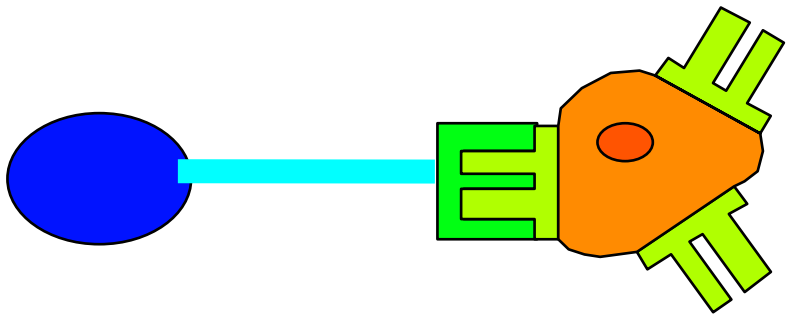
Your body and brain are full of nerves which transmit and receive information electrically, producing magnetic fields that provide a window into their function.

Even if the process we are interested in isn't magnetic, sometimes we can make it magnetic

Take tiny magnetic beads, smaller than a blood cell, and use them to label cancer.

This provides you with a tool for looking for cancer by looking for where the magnetic signal is.

You can even try to use these magnetic beads to kill the cancer.



Magnetic particle bound to cell

The SQUID team

Robert Kraus, Michelle Espy, Andrei Matlachov, Val Armijo, Shaun Newman, Dave Clark, Carl Kumaradas, Petr Volegov, Mark Peters

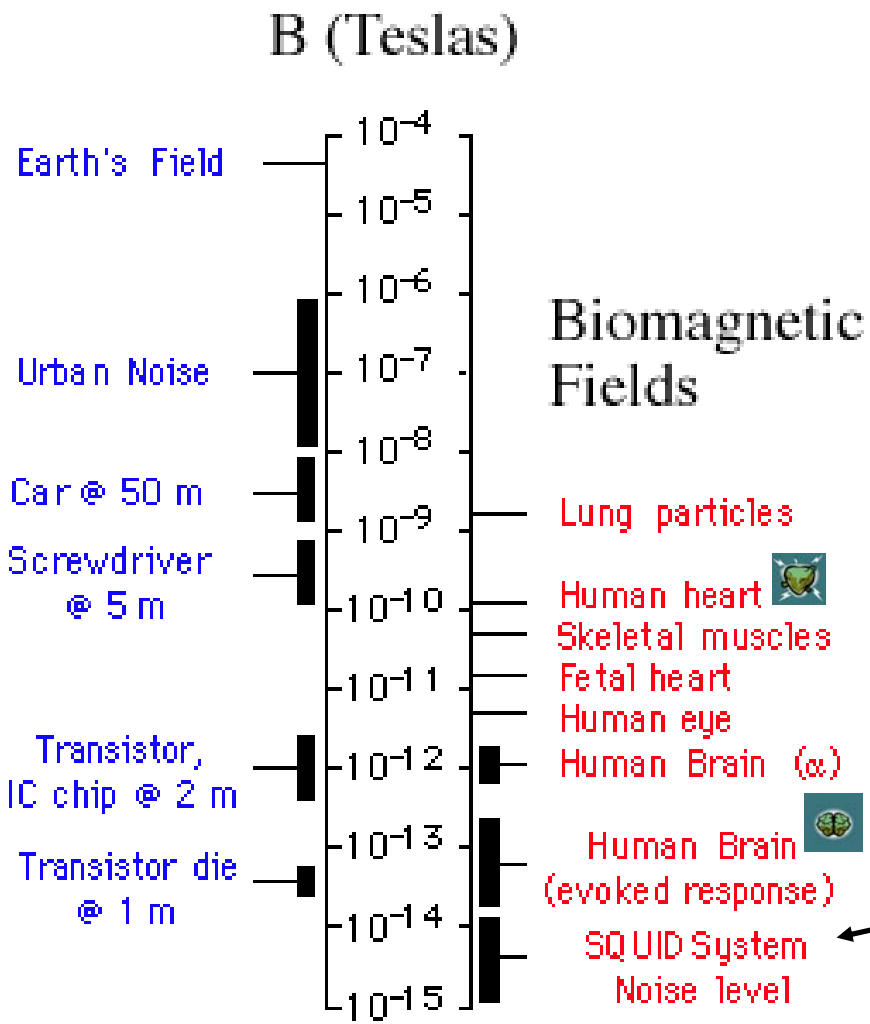
Students: Anne Chamberlin (LAHS/Lewis and Clark), Shawn Forrest (U. Utah), Jessica Lamb (Dartmouth/Cornell), Jonatan Mattson (U. Chalmers, Sweden), Walter Roybal (UNM/Pojoaque). We are ALWAYS looking for students!

External Collaborations: UNM, VA Hospital, U. Nebraska, MIND Inst. etc.

Biggest magnetic fields (NHMFL)

Magnetic Fields

This scale is logarithmic (like the Richter scale for earthquakes) so each division indicates a magnetic field 10 times larger than the one below it!



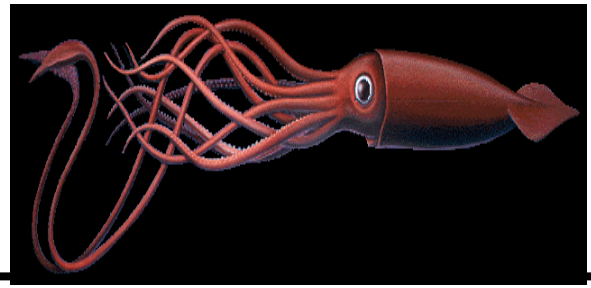
The sensitivity is both the best and worst things about a SQUID – and why they aren't very common

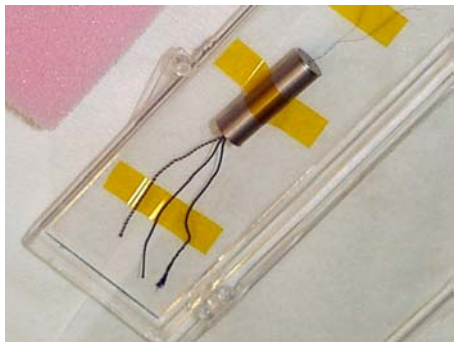
If SQUIDs are so great, why aren't they everywhere?

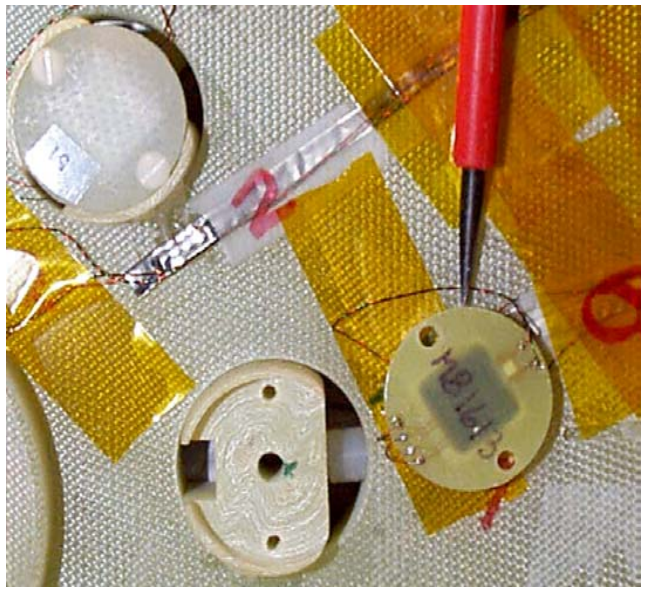
Some systems mentioned tonight have electrical counterparts (EKG for hearts, EEG for brains) that are more common. Why?

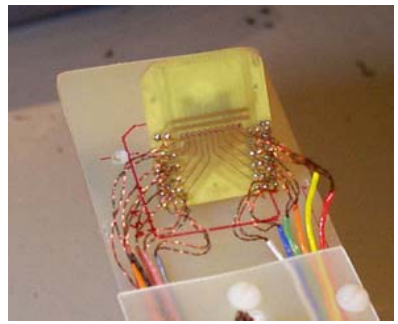
Because SQUID systems are harder to build.

Superconducting Quantum Interference Device







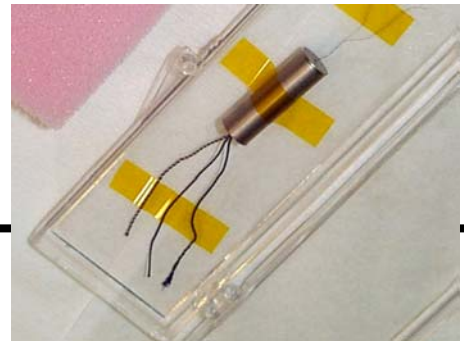


The devices are ~1” in size – but most of that is packaging – places to connect to.

Actual SQUID sizes are on the order of 10-100 microns (like a human hair).

They are made very much like regular computer chips, but with superconducting material.

SQUIDs are tools



The SQUID team is an instrumentation team: we build systems that use SQUIDs as tools to measure the magnetic fields associated with processes of interest:

The heart – function when healthy, or diseased.

The human brain – localizing function for surgery, epilepsy, effects of illness, how the brain is organized and processes information.

Cancer – early detection and diagnosis, better treatments.

Bioassay- Looking for DNA sequences, viruses, pathogens.

Measuring Small Magnetic Fields in Living Systems: from Understanding the Brain to Cancer Detection.

Magnetic fields provide the clues to the biological processes.

SQUIDs can measure these fields totally non-invasively:

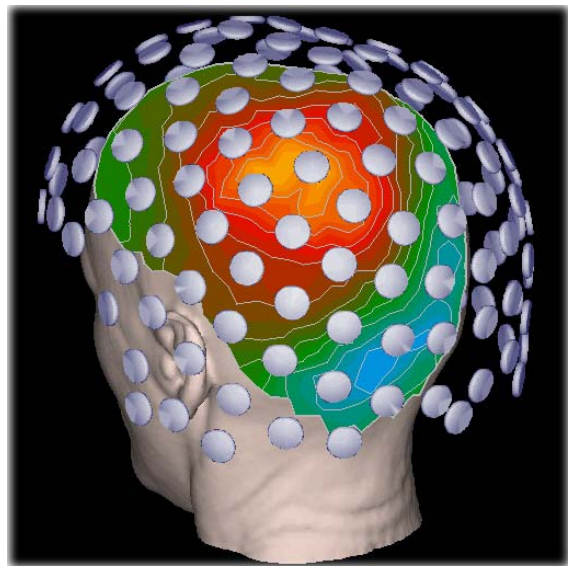
nothing touches you

no radiation

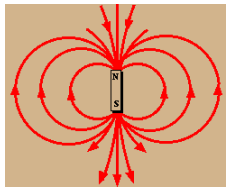
not loud

doesn't hurt

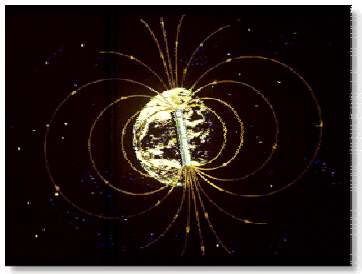
no injections



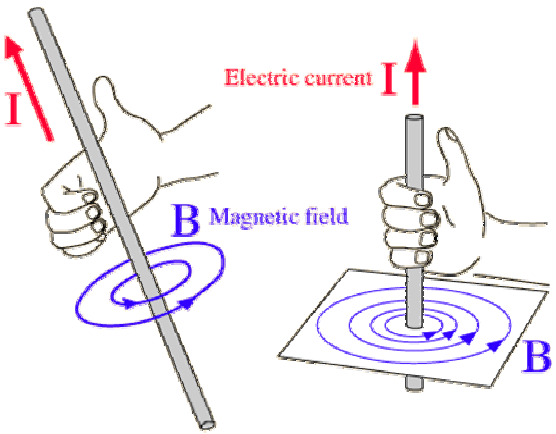
Magnetic Fields: they are all around us



Bar magnet (refrigerator magnet), Strong on surface, but goes away quickly with distance.



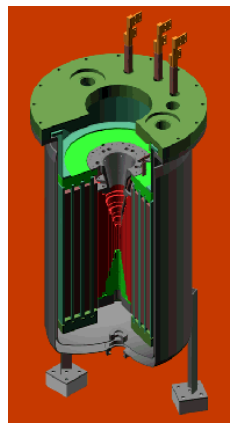
Magnetic field of the earth. 10,000 smaller than a refrigerator magnet, but we see it's effects: i.e. the compass.



Current will produce a magnetic field that is proportional to its size. CD player power adapter cord at 10 inches has field a million times smaller than the field of refrigerator magnet.

MRI systems, ~10 times stronger than refrigerator magnet, over a large area. Produced by large currents. Often the magnets are superconducting, meaning that they are kept VERY cold and the big currents flow without resistance.

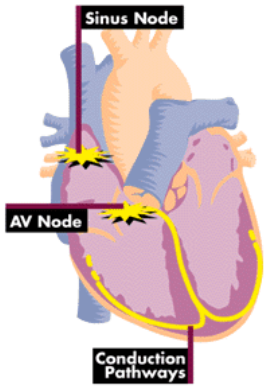
National High Magnetic Field Laboratory (Los Alamos, Florida State, U. Florida) has magnets that produce fields 100 – 1000 times stronger than the fields from a refrigerator magnet



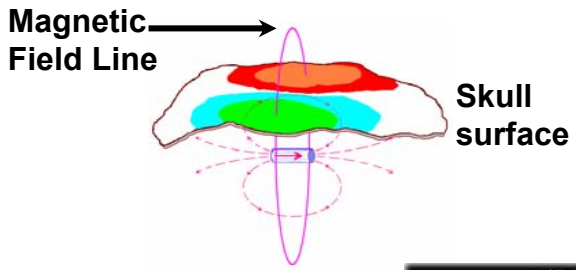
NASA Los Alamos

Physics

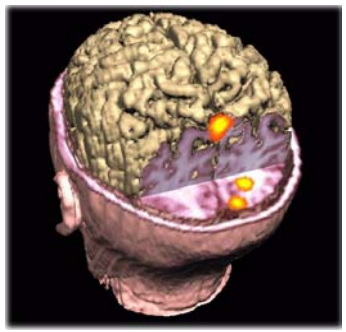
Small Magnetic Fields in Living Systems: really small!

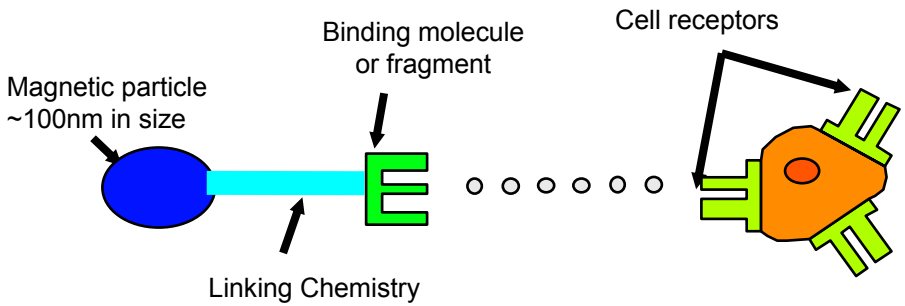


Magnetic field from electrical activity in the heart (a billion times smaller than the refrigerator magnet's field)



Magnetic field from electrical activity in the brain (roughly a trillion times smaller than the magnetic field from your refrigerator magnet)



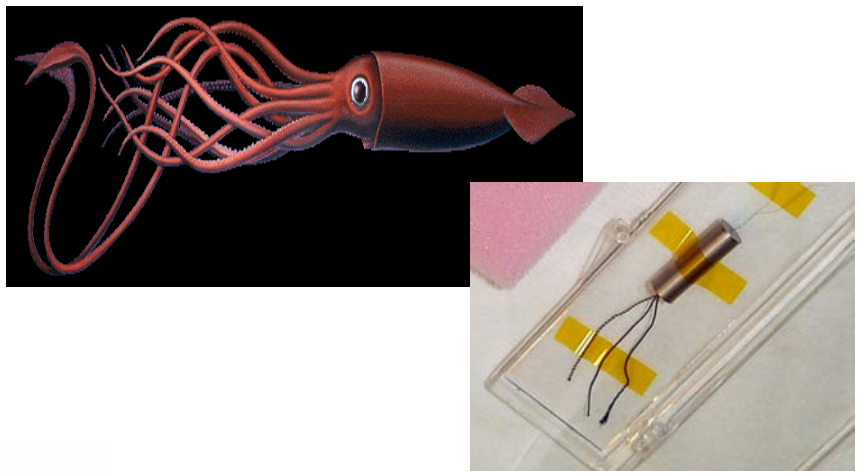


Tiny magnetic particles can be attached to an agent that seeks a certain type of cell receptor, i.e. cancer. This gives the cancer a magnetic label about a billion times smaller than the magnetic field from a refrigerator magnet when you measure on the surface of the body.

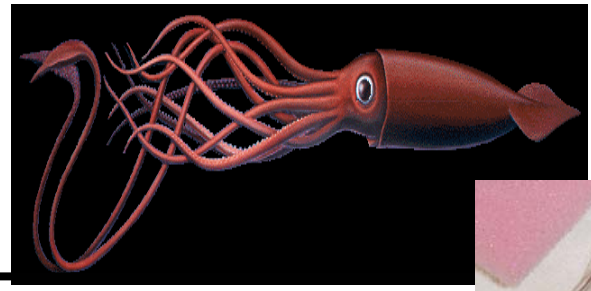
Measurements with SQUIDs

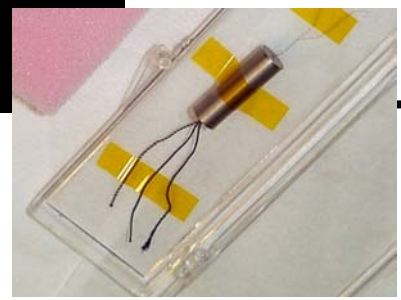
We use small passive detectors called SQUIDs, superconducting quantum interference devices, to detect these magnetic fields.

The SQUID is the most sensitive detector of magnetic fields known, capable of measuring magnetic fields billions of times smaller than the magnetic field of the earth.



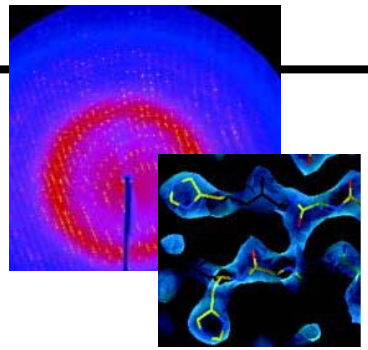
Outline



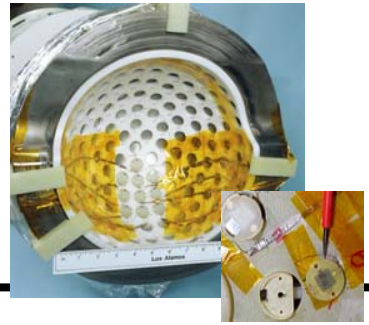


- Introduction to the Biophysics Group
- Introduction to SQUIDs
- What we do with SQUIDs (biological applications)
  - Heart function
  - Brain Function
  - Magnetic Cancer detection and treatment
  - Bioassay

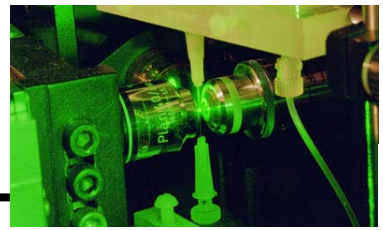
The Biophysics Group



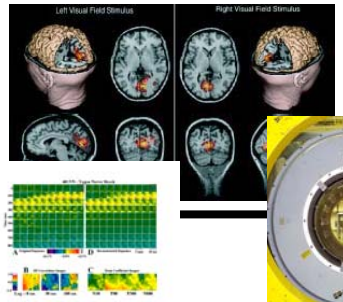
Protein Crystallogarphy



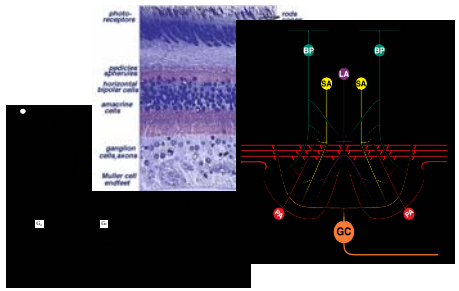
SQUID applications



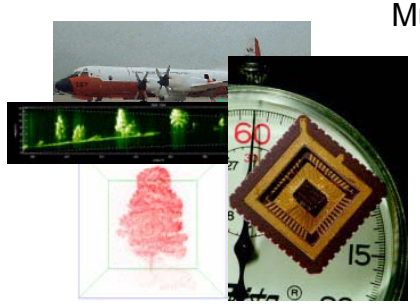
Biomolecule detection



Multi-modality brain imaging



Computational Neuroscience



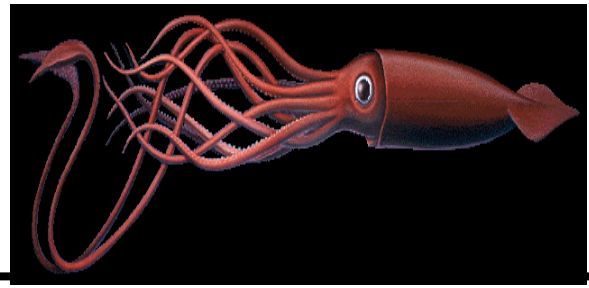
High Speed Electronics

- **Who we are**
  - ***Physicists, Physiologists, Neuroscientists, Mathematicians, Technicians, Computer Scientists, Electrical Engineers, Support Staff , Students….***

- **Our Mission**
  - ***Contribute to the understanding of biological phenomena by means of the scientific, technical, and conceptual resources of Physics***

NNSA Los Alamos

Physics



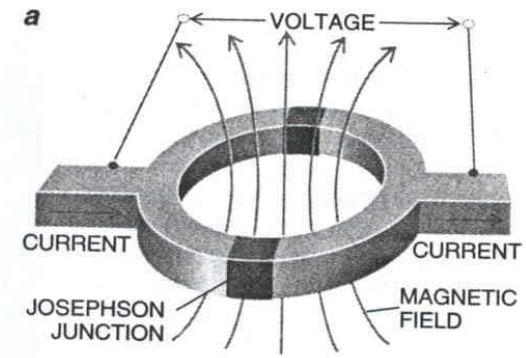
What is a SQUID anyway?

S is for Superconducting

A SQUID is made up of a loop of superconductor: current (electrons) flow with no energy loss or resistance.

In normal metal electrons bump into atoms and lose energy as they flow (resistance – or why a light bulb lights). In a superconductor the electrons don't bump into anything, and current flows with no loss.

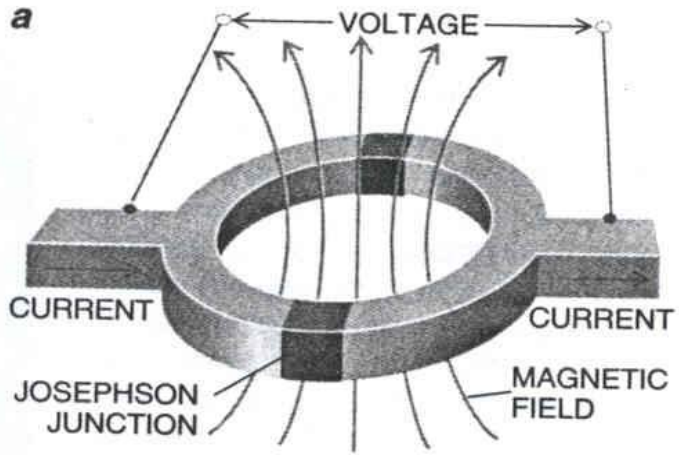
But a SQUID is a superconductor with a twist (or two).
A SQUID has two spots that are not good superconductors. They are like kinks in a hose – so at some current the electrons can't get through without bumping. And you get resistance, which can be measured as a voltage across the SQUID.

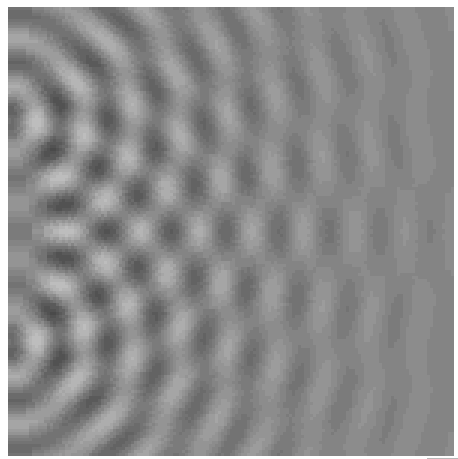


Q is for Quantum
I is for Interference

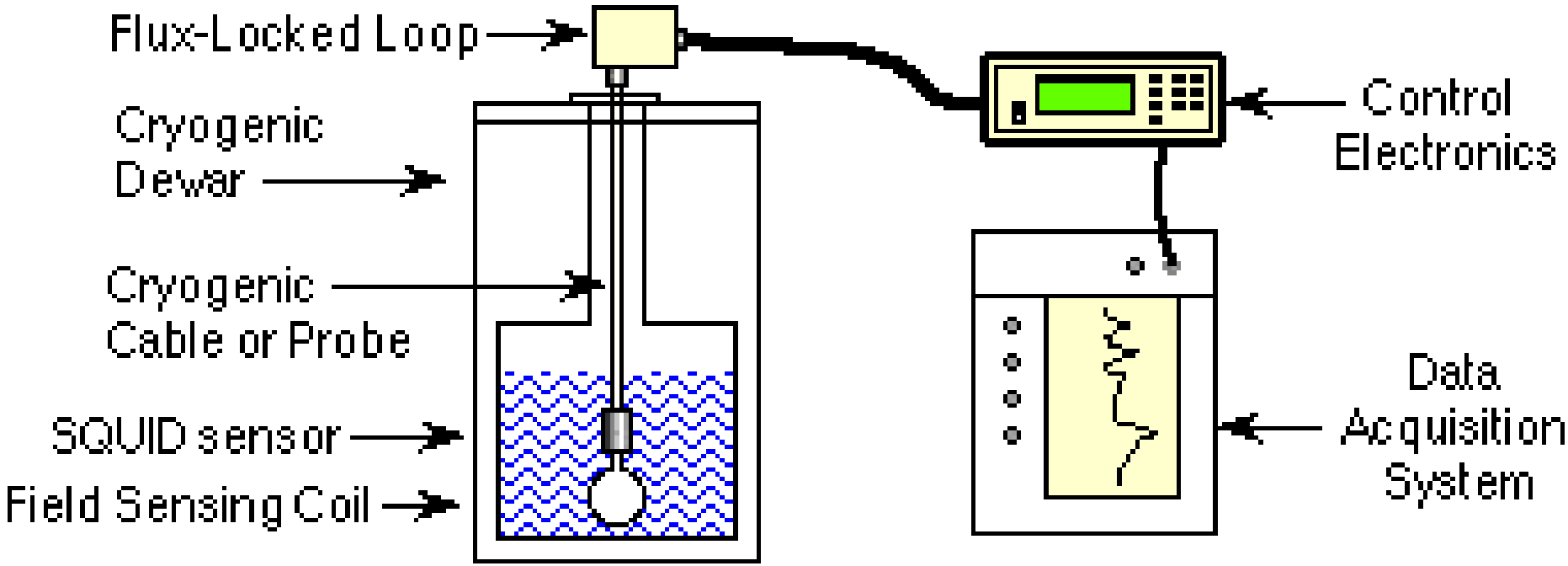
The electrons are also like waves (that's Quantum Mechanics). So you have the same effect from the two "kinks" in the SQUID that you have dropping two pebbles into water – wave interference.

The waves also depend on the magnetic field through the SQUID. This makes the voltage change depending on the magnetic field. SQUIDs can detect changes in magnetic field a million times smaller than the magnetic field of the earth passing through an area the size of a red blood cell.





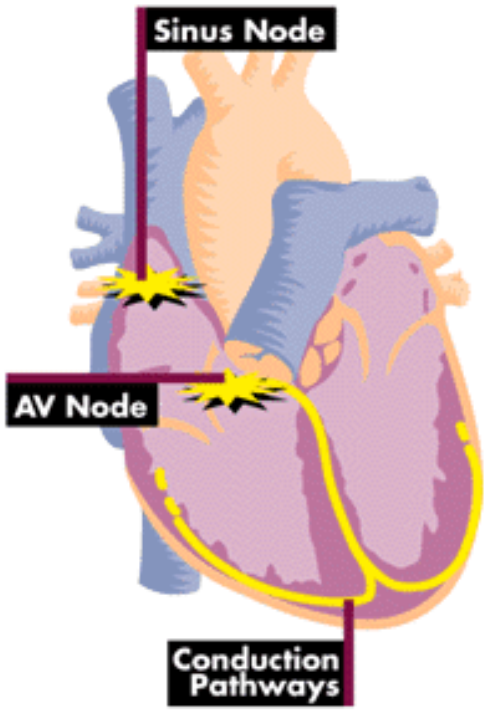
D is for device: the basics of a SQUID system

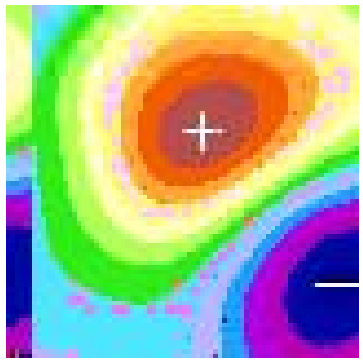


All SQUIDs must be cold, and are usually cooled with either liquid helium (- 452 F) or liquid nitrogen (- 321 F). The temperature of the surface of Pluto is – 378 to – 396 F

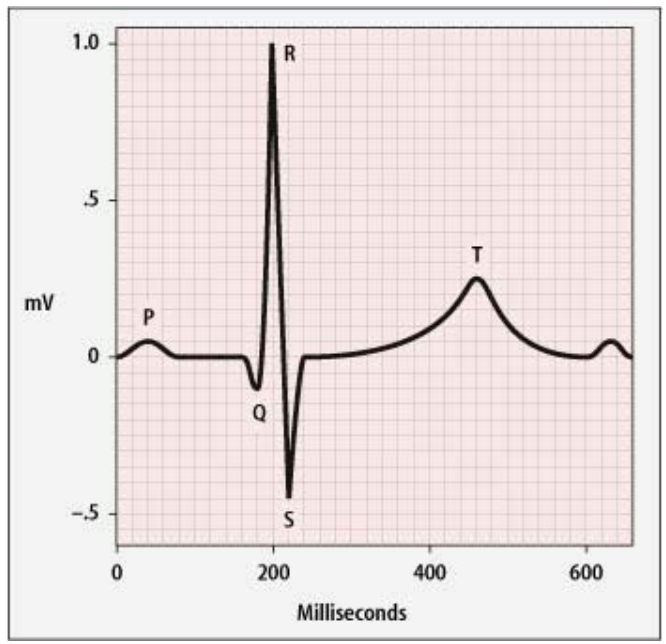
Functional Heart Imaging with Magnetocardiography (MCG)

The heart is electrical and the magnetic fields we measure have the same source as electrocardiography: ECG or EKG





Magnetic field map above a beating heart



QRS complex of a healthy heart

Functional Heart Imaging with Magnetocardiography (MCG)

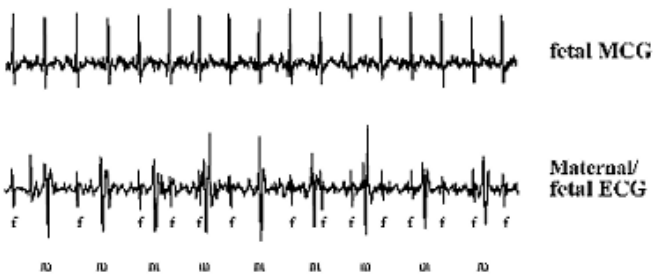
EKG is more common and electrodes are less susceptible to problems with external magnetic signals. Why do MCG instead of EKG?

Non-contact, less preparation (mass screening, burns)

Complementary information, no signal losses in tissue

May be more sensitive to certain conditions

Fetal MCG – there is no good electrical way to measure the QRS of the fetal heart

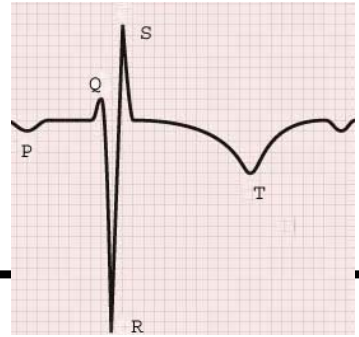


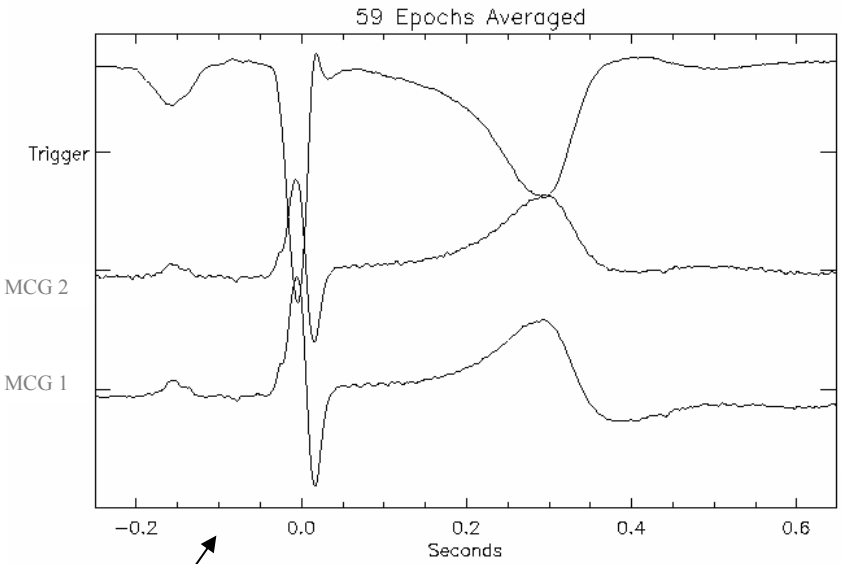
EFMT, Bochum

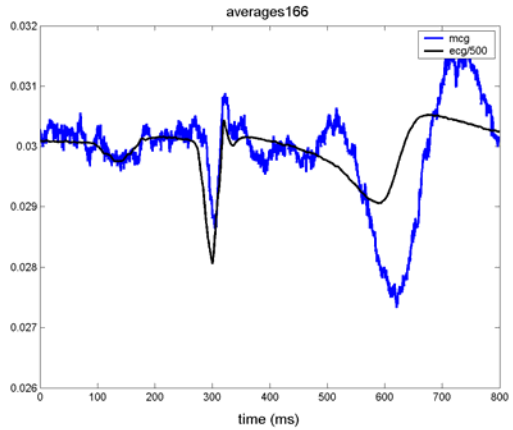
with permission: CTF, Canada

At Los Alamos we have used our computational resources to help solve problems like removing the mother's heart beat from a fetal MCG signal.

MagnetoCardiography (MCG)



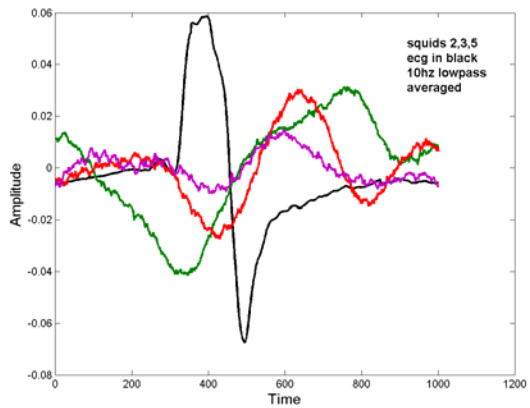




liquid nitrogen

liquid helium

Frog MCG



NNSA Los Alamos

Physics

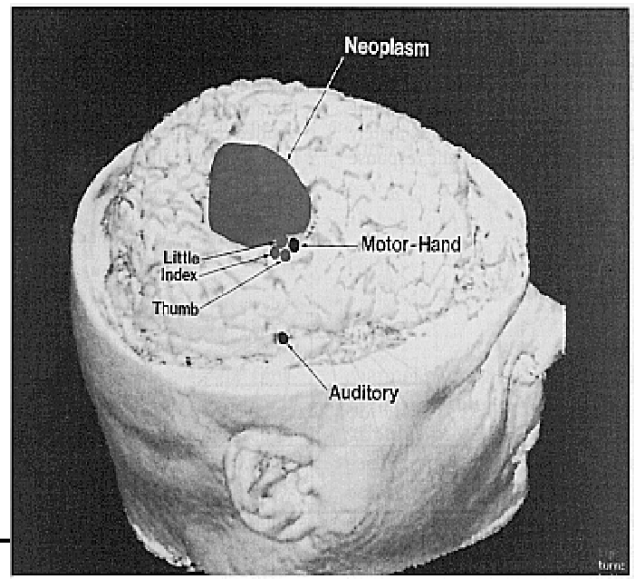
Functional Brain Imaging with Magnetoencephalography (MEG)

Use magnetic field information to probe where function is located and the timing of function. Why is this type of imaging important?

Study Brain Function: **How, When, Where does the brain respond to stimuli?**

Diagnostic Tool: **Diagnose epileptic spikes and locate where they are initiated. Locate a region of brain injury.**

Pre-surgical Localization: **'Map' primary brain centers prior to surgery.**

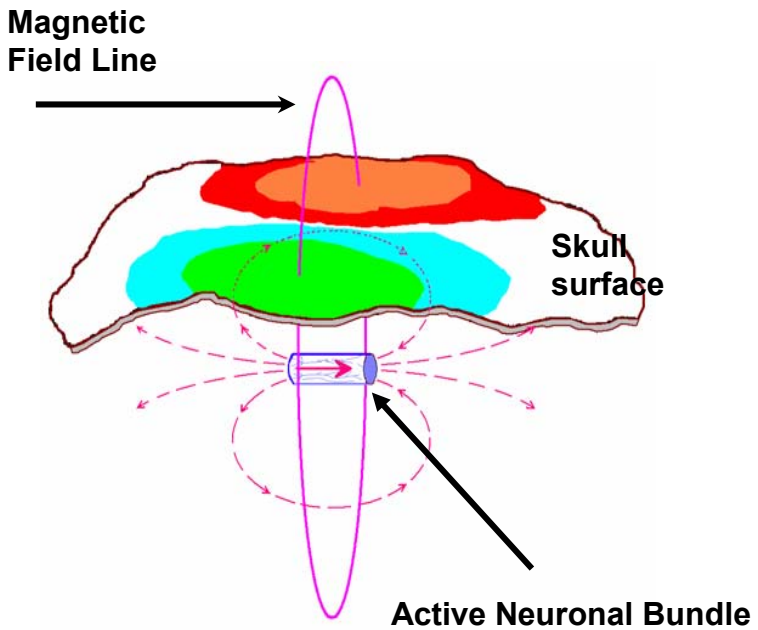


Functional Brain Imaging with Magnetoencephalography (MEG)

MEG/EEG measure responses directly from neurons. MEG is similar to EEG, but less common. Which is better? Ideally you would do both.

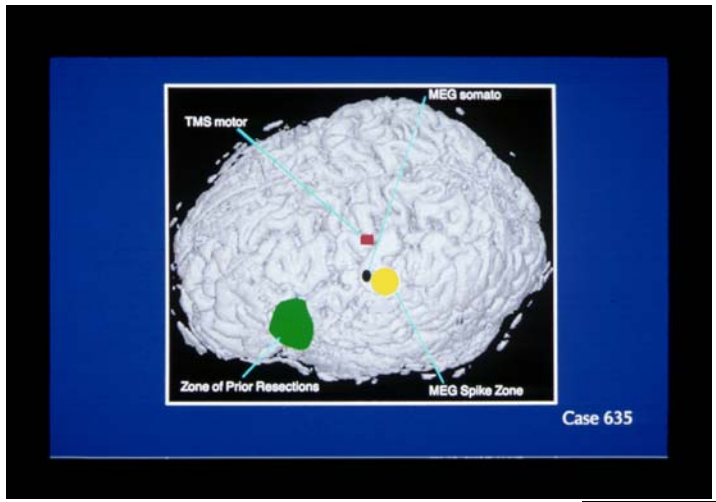
There are other methods to study brain function.
Implanted electrodes (invasive).
PET (radioactive)
and fMRI, like an MRI

PET and fMRI only tell you about blood flow, which is slower (~1 sec) than neuronal activity (1/1000 sec).

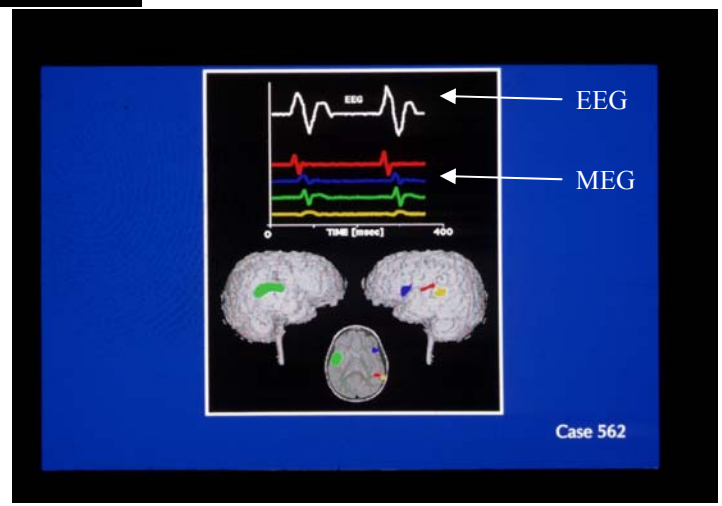


What good is the timing information?

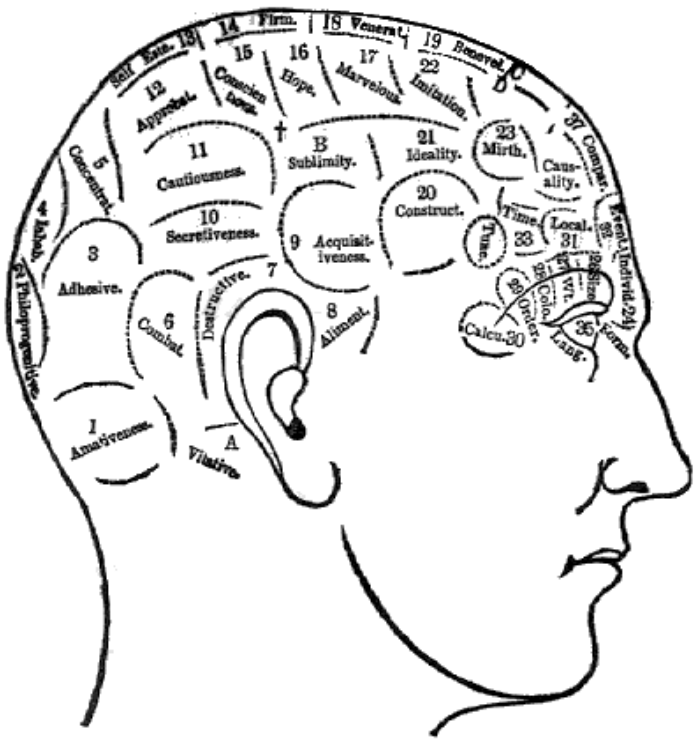
- Sources of epilepsy



- The effects of medication on the brain
- How the brain recovers from injury
- How the brain is processing information



Early ideas of how the brain worked….



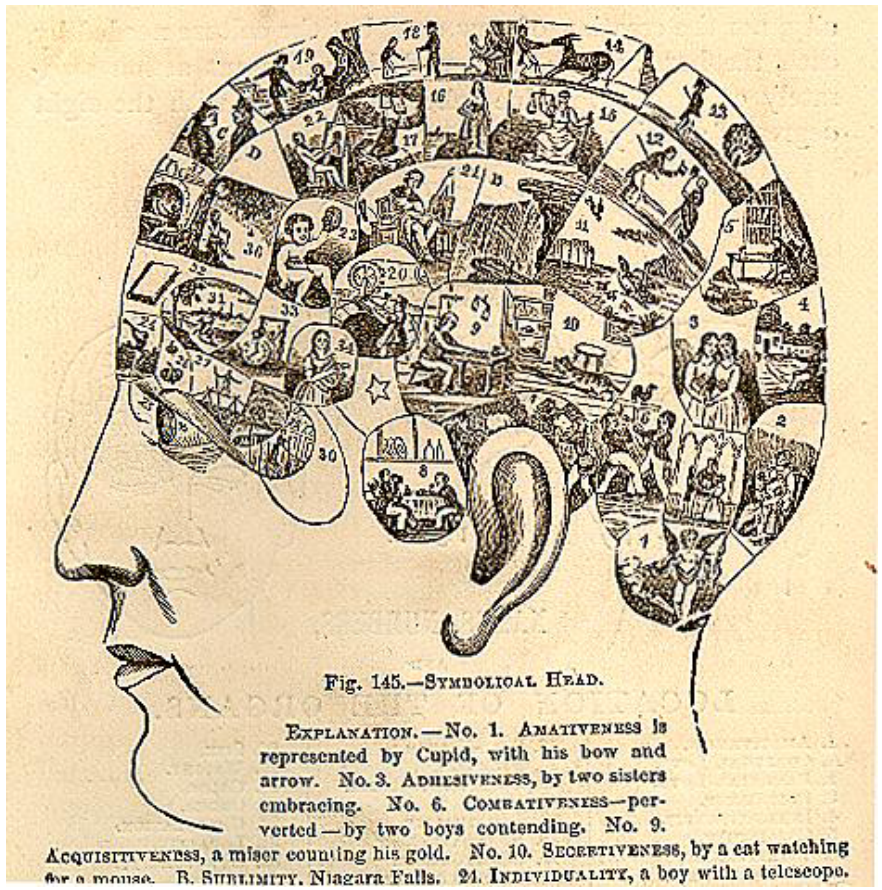
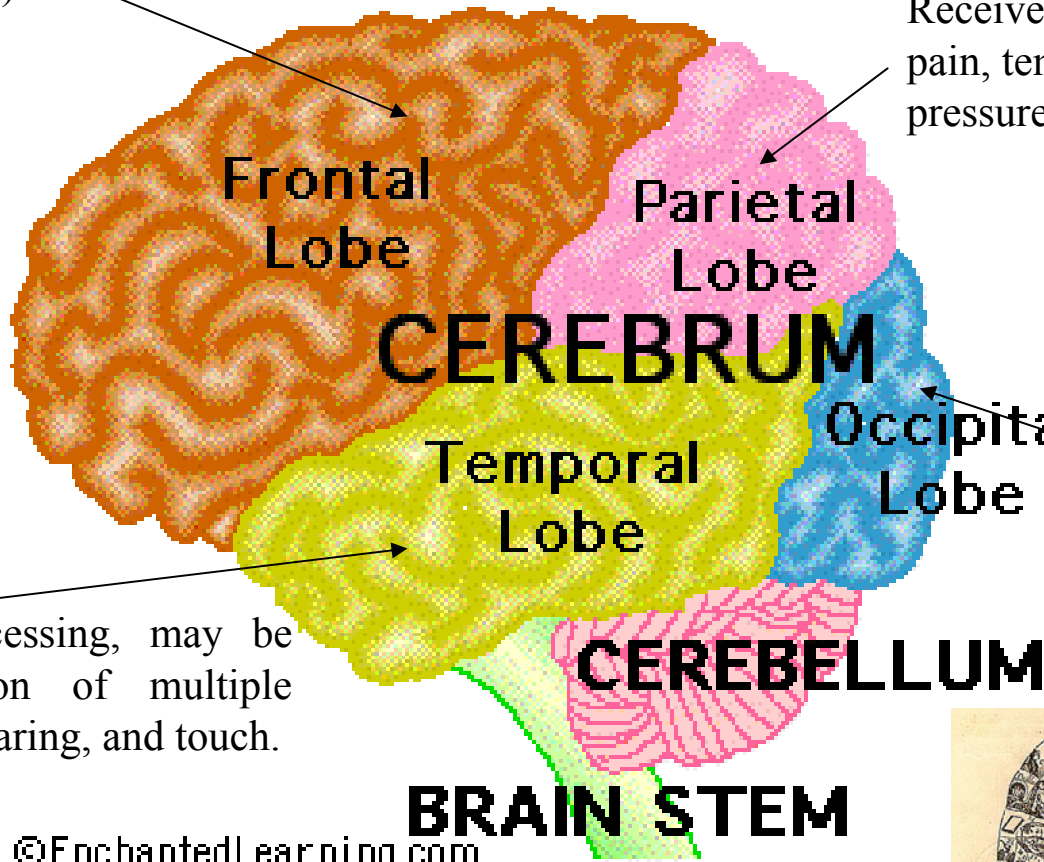


Fig. 145.—Symbolical Head.

Explanation.—No. 1. Amativeness is represented by Cupid, with his bow and arrow. No. 3. Adhesiveness, by two sisters embracing. No. 6. Combativeness—perverted—by two boys contending. No. 9. Acquisitiveness, a miser counting his gold. No. 10. Secretiveness, by a cat watching for a mouse. B. Sublimity. Niagara Falls. 21. Individuality, a boy with a telescope.

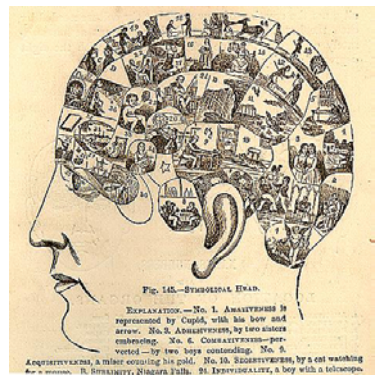
Planning ahead, prediction, speech (lower mostly left), motor (thin strip in front of central sulcus)

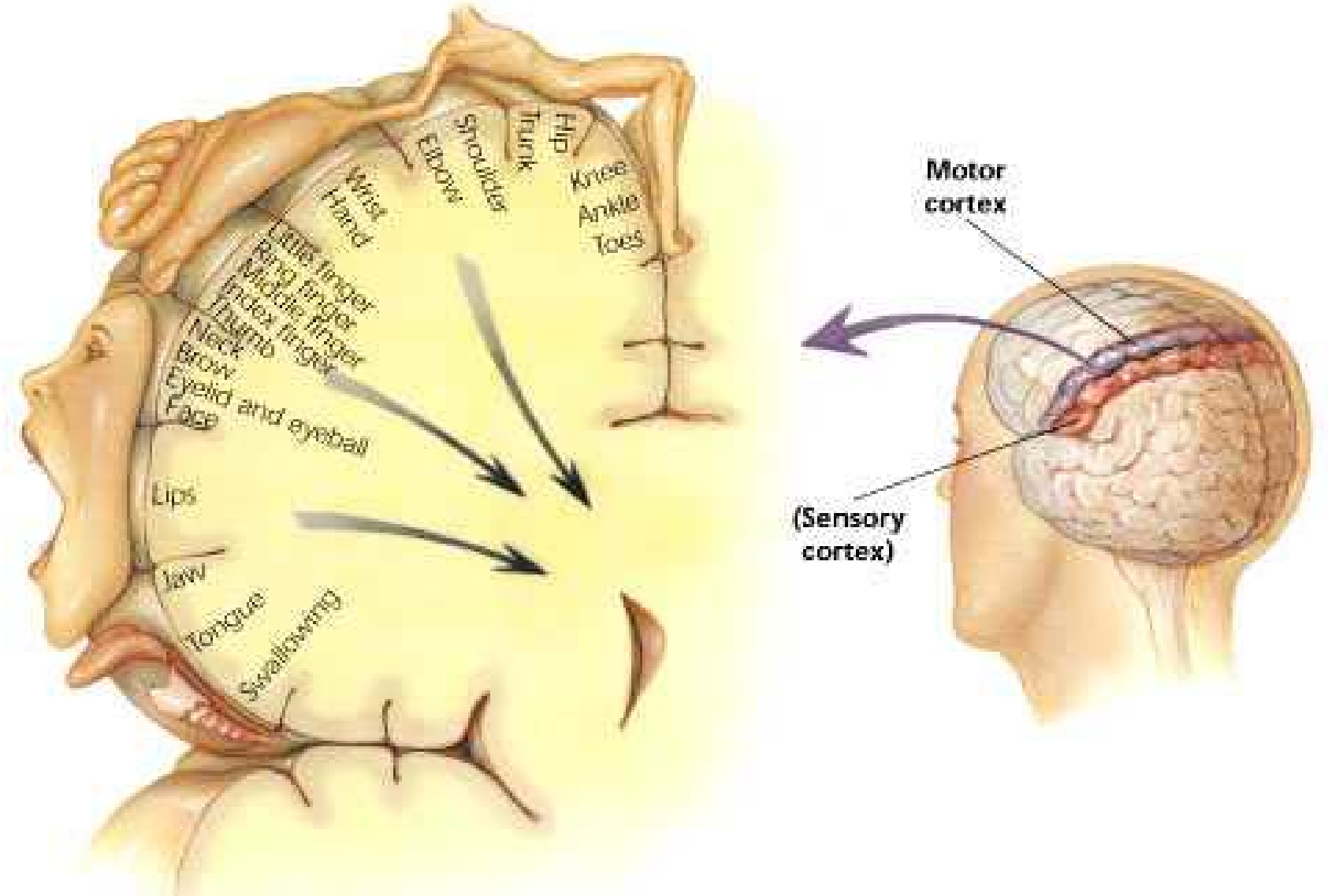
Receives nerve impulses for pain, temperature, touch, and pressure: primary sensory area.



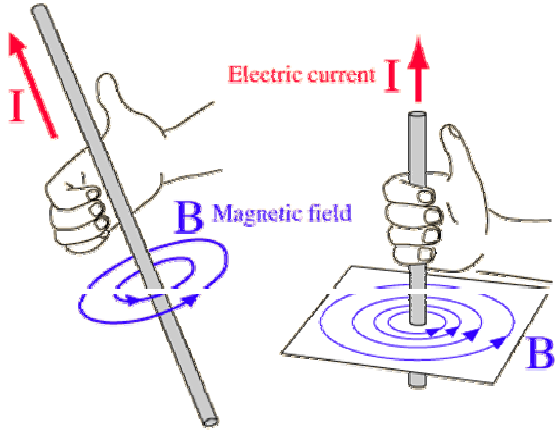
Visual information

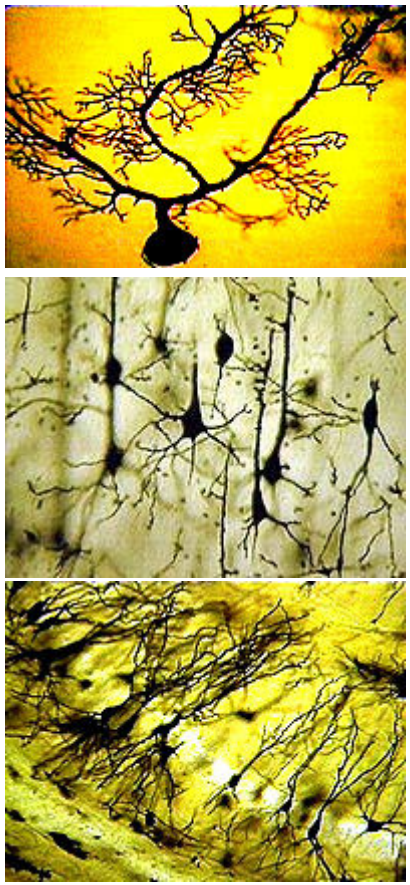
Hearing, memory processing, may be involved in integration of multiple sensory functions i.e. hearing, and touch.



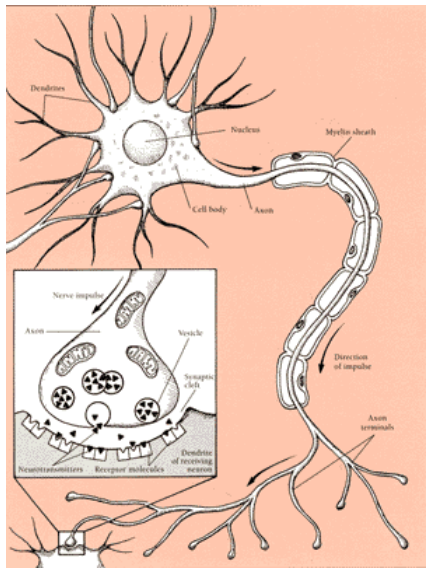

Hip
Trunk
Shoulder
Elbow
Wrist
Hand
Little finger
Ring finger
Middle finger
Index finger
Thumb
Neck
Brow
Eyelid and eyeball
Face
Lips
Jaw
Tongue
Swallowing
Knee
Ankle
Toes
Motor cortex
(Sensory cortex)

The Brain is electrical, and thus magnetic

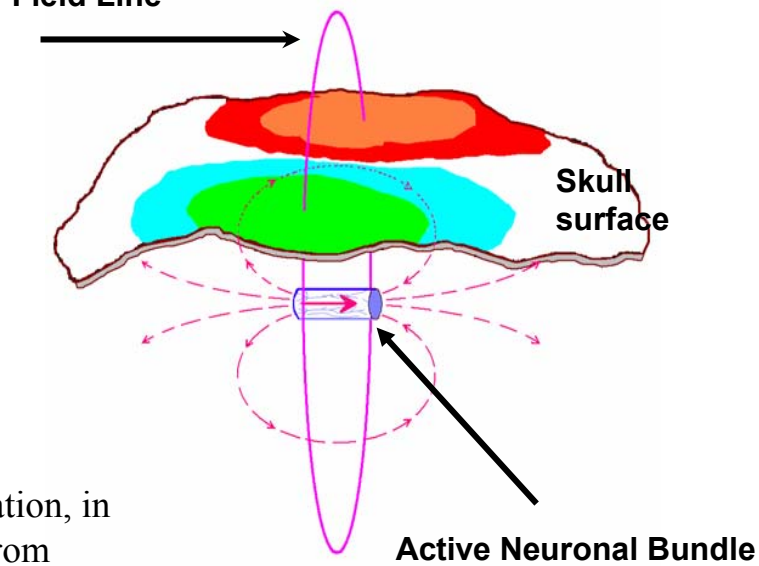




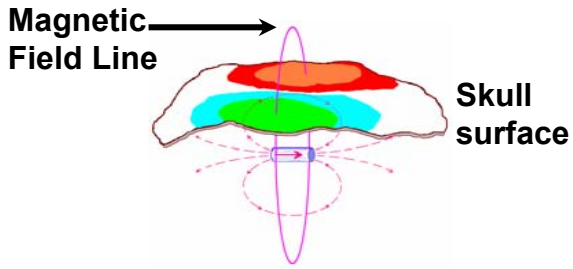
The brain is full of nerve cells



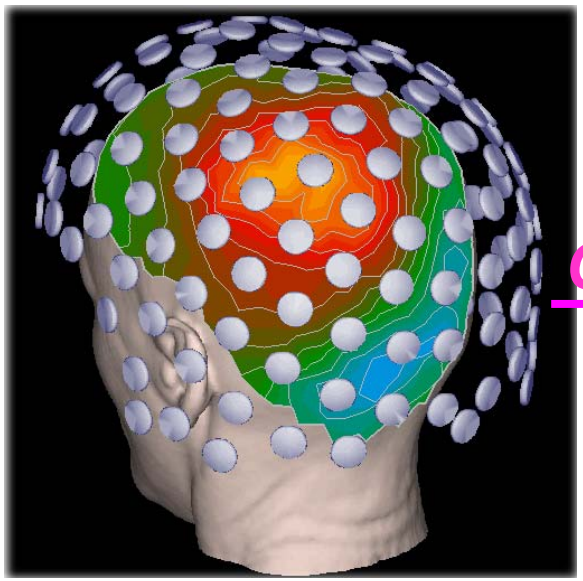
The nerve cell receives information, in the form of electrical signals, from other cells through connections or synapses on its dendrites and sends information by way of its axon.



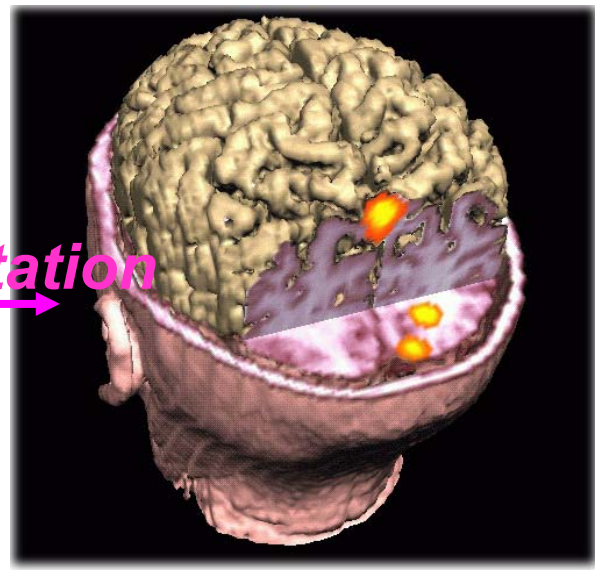
Magnetoencephalography MEG



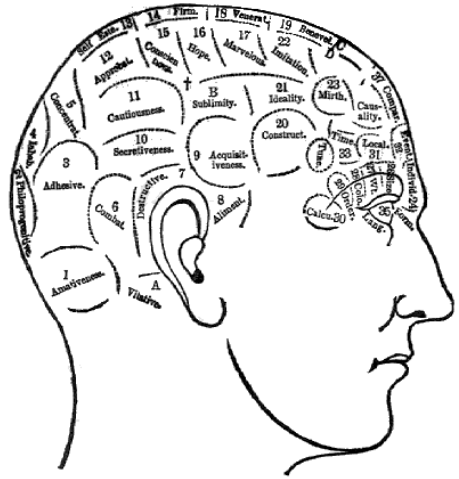
SQUIDs measure magnetic fields outside of the head due to neuronal activity



Computation



Mapping Brain Function… and more



- **Where function is located**
  - **pre-surgical, site of epilepsy**

- **The time course of activity**
  - **faster than 1/1000 of a second responses directly from neurons**

- **To understand how the brain processes information and what this means to healthy brains and in the treatment of disease**

LANL MEG System

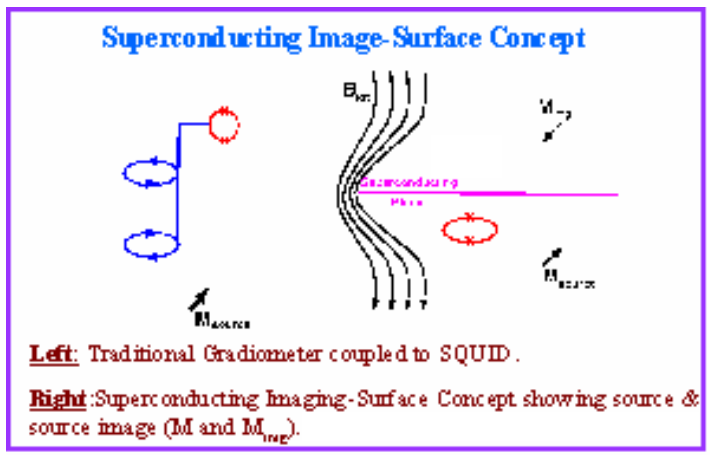
Totally passive measurement, no noise, radiation, head restraints, etc.

The Los Alamos MEG system

MEG systems are available commercially – but ours is different

Most systems use a series of complicated coils and expensive shielded rooms to reduce background fields.

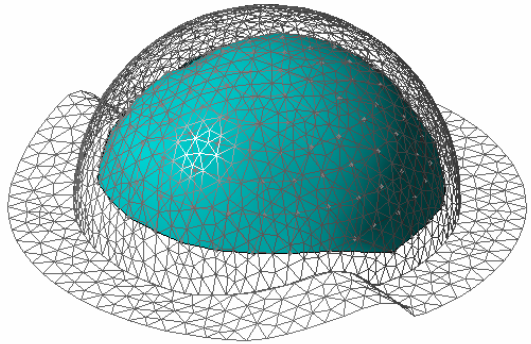
Our system has a superconducting shield built in – which means you don't need the coils or as expensive of a shielded room

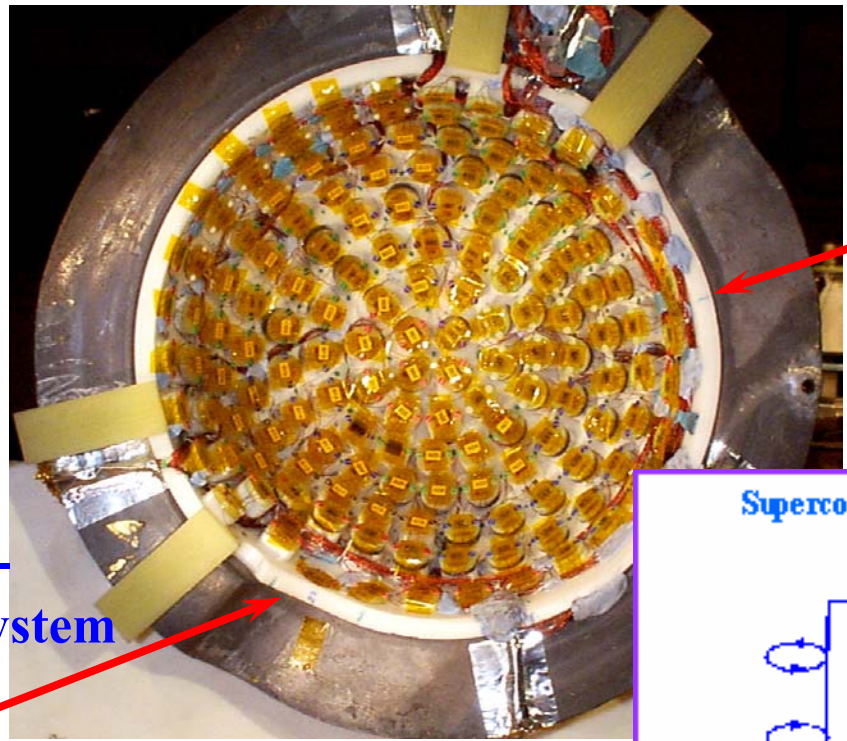


Left: Traditional Gradiometer coupled to SQUID.

Right:Superconducting Imaging-Surface Concept showing source & source image (M and M_{img}).

The Los Alamos MEG system

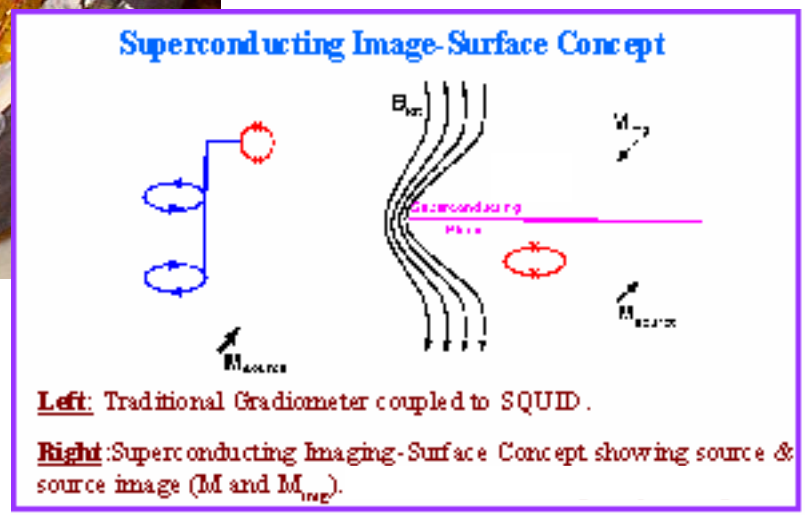




Corian®-like support and mounting structure. (DuPont/LANL Patent)

The LANL Whole-Head SIS-MEG System

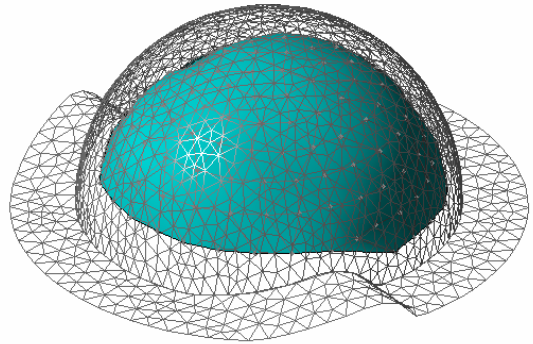
Lead Superconducting Imaging Surface (SIS) "helmet".

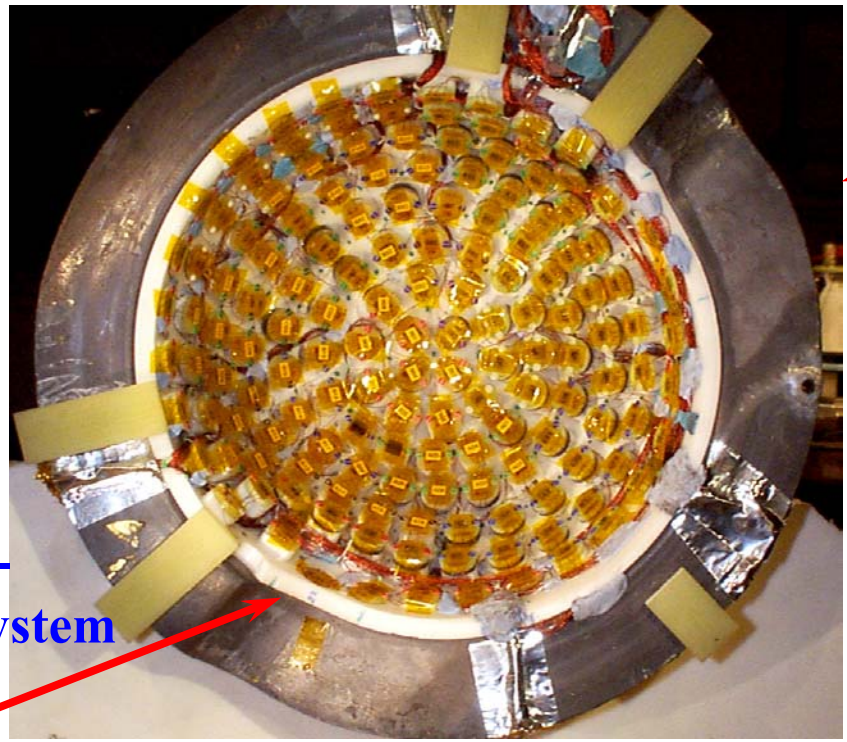


NNSA Los Alamos

Physics

The Los Alamos MEG system





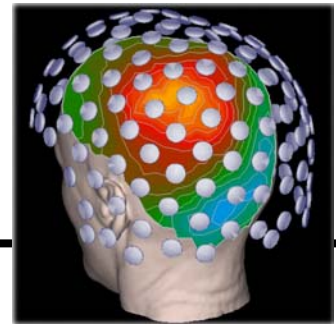
Corian®-like support and mounting structure. (DuPont/LANL Patent)

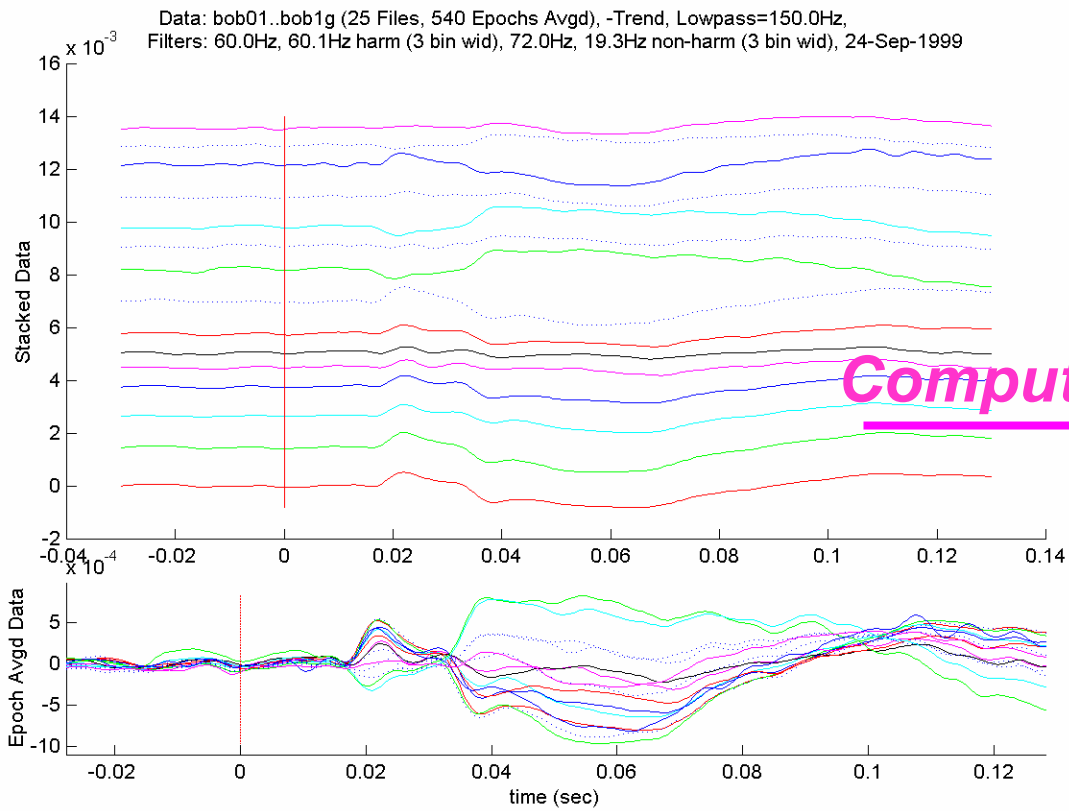
The LANL Whole-Head SIS-MEG System

Lead Superconducting Imaging Surface (SIS) "helmet".

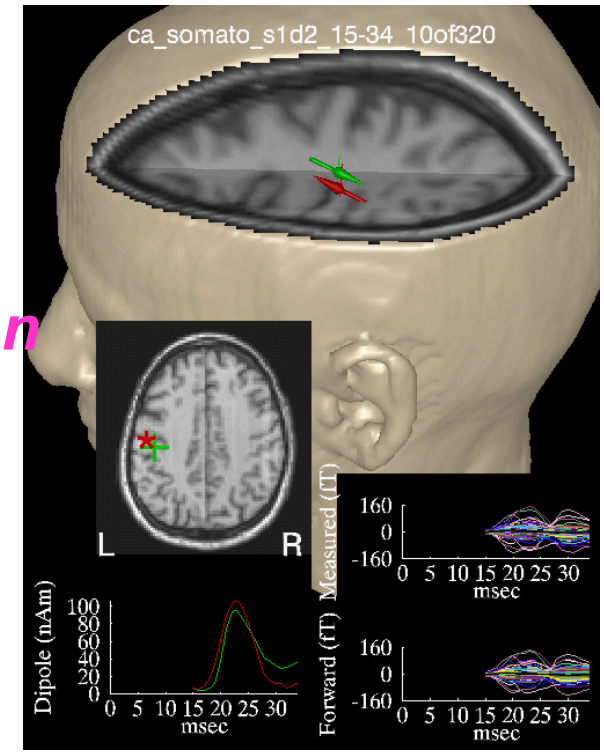
The cryogenic column is immersed in liquid helium at 4K

From raw data to results

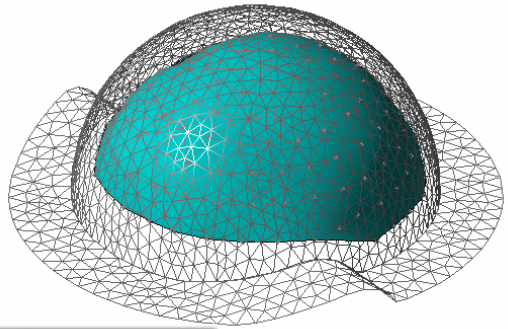


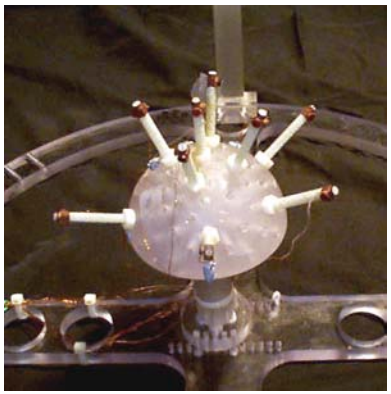


Computation

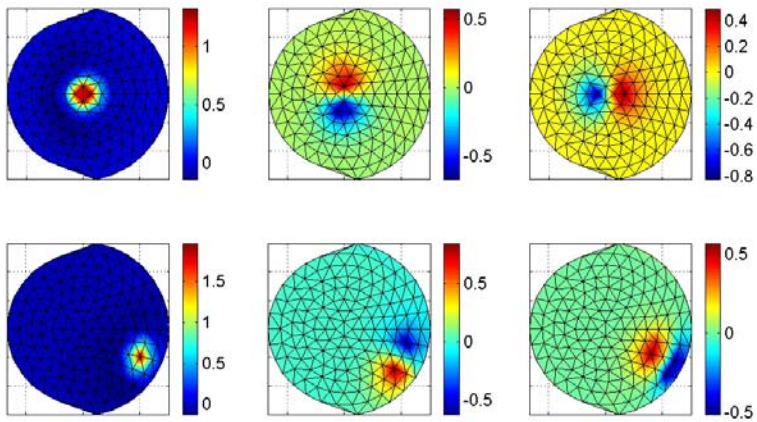


Calibration with precision phantoms

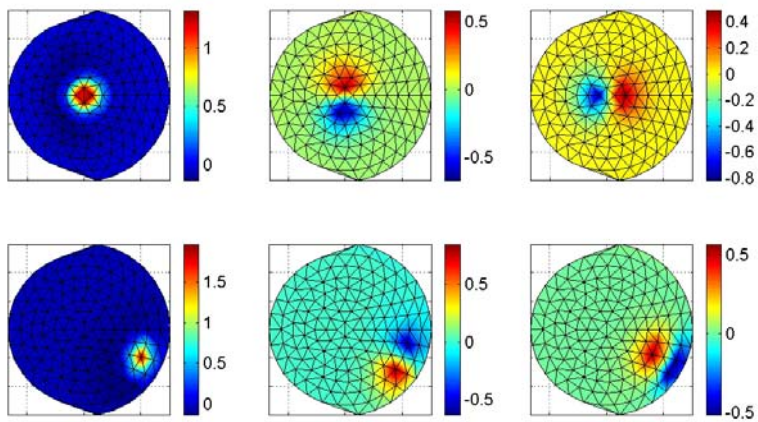




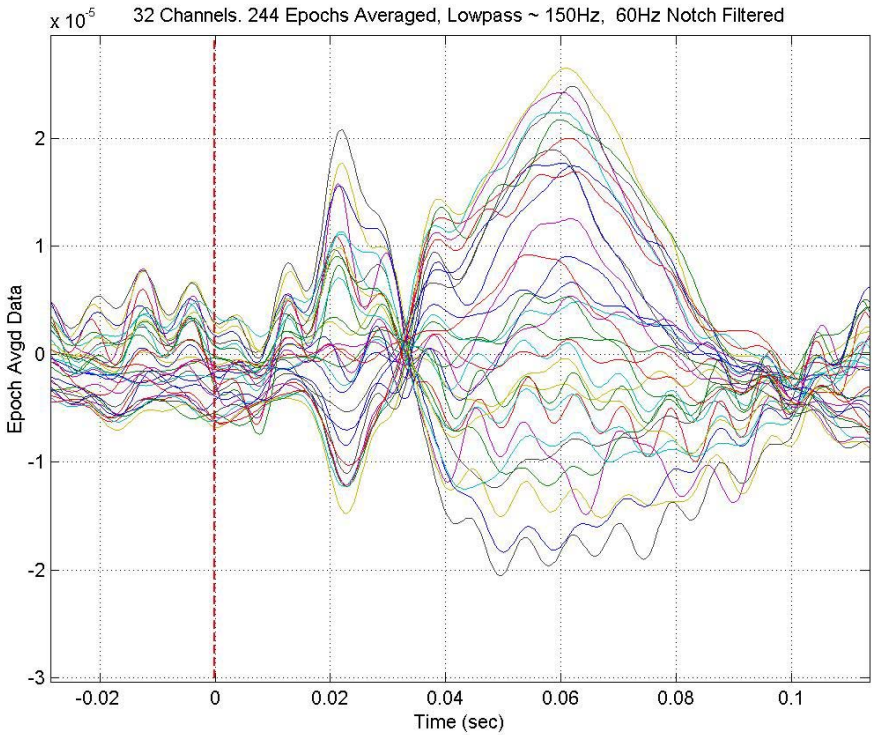
Experimental data

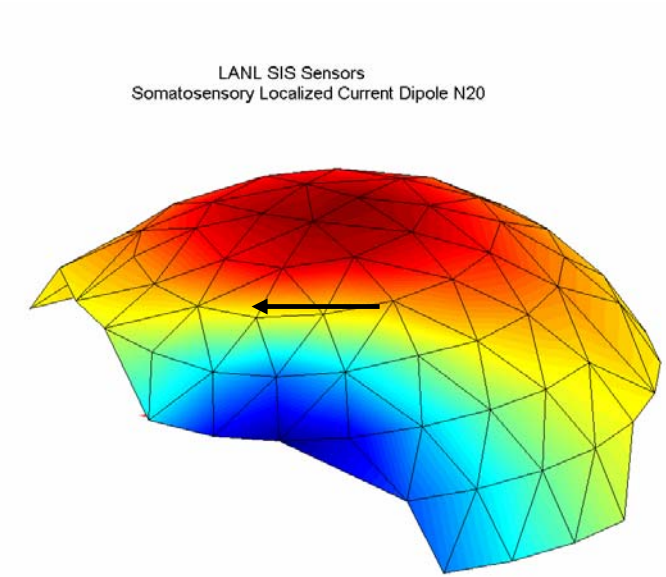


Model data after CS transf. Rz[16.9] T[-0.2 0 -1.1]



From raw data to results





Where To Next?

- System is at the VA Hospital in Albuquerque for performance studies
  - The VA hospital has a commercial system that they use for epilepsy, pre-surgery, and other studies.
  - We want to compare our system to theirs
  - first tests with both phantoms and people
  - Our system will be as good (better) and need less shielding

- At present our spatial resolution of phantom sources is 1/100 of an inch (better than the best reports in the literature)

- We are extremely pleased!

Why are we doing MCG or MEG?

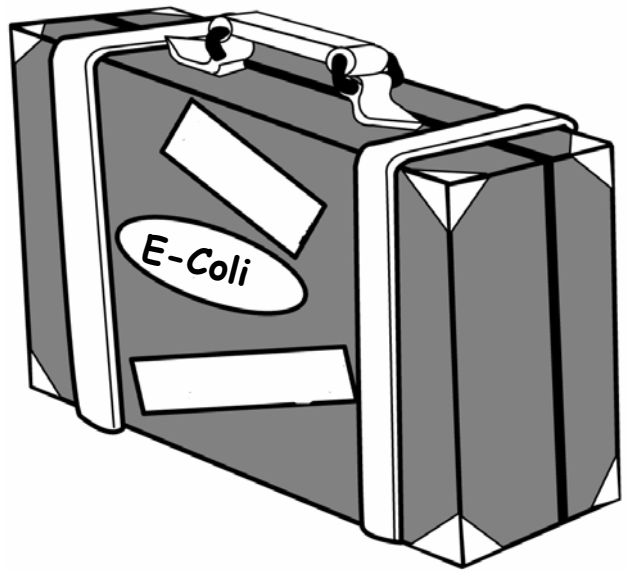
- Systems exist commercially, but at Los Alamos we have the resources and to try and push the technology in new directions.

Bioassay and MagnetoCarcinotherapy: labelling what you are interested in with tiny magnetic particles

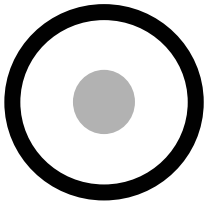
- In collaboration with
  - University of Nebraska, University of New Mexico, Bioscience Division, Spallation Neutron Source Division, Chemistry Division

- Small (bacteria sized) magnetic particles (labels) attached to agents that seek out and label specific biological targets

- SQUIDs to detect and/or image particles

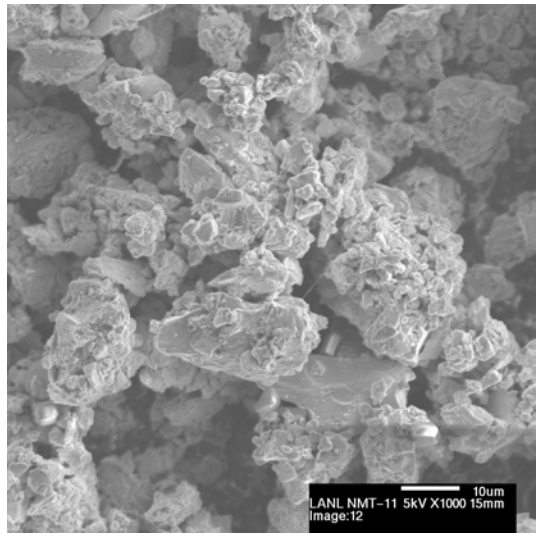


The material must be coated, sorted, and attached to the right agents.



Polymer bead with diameter about 1/10th – 1/100th of a hair

Magnetized core with diameter about ½ that size

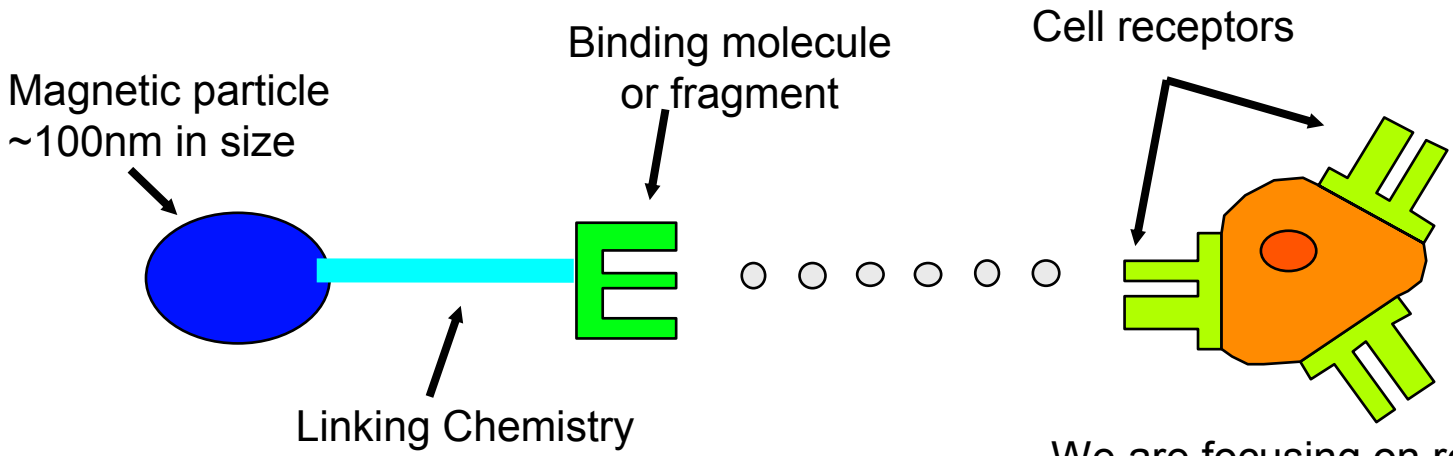


A magnet made of this material is 10 times stronger than your average refrigerator magnet of the same size.

This step of attaching the labels to something that is specific only to a certain type of cell (cancer) or DNA fragment, etc. is an active area of research – its called molecular targeting.

Both of the next two projects I will discuss are VERY new and involve using these magnetic labels to monitor biological processes.

Carcinotherapy: Target the cancer

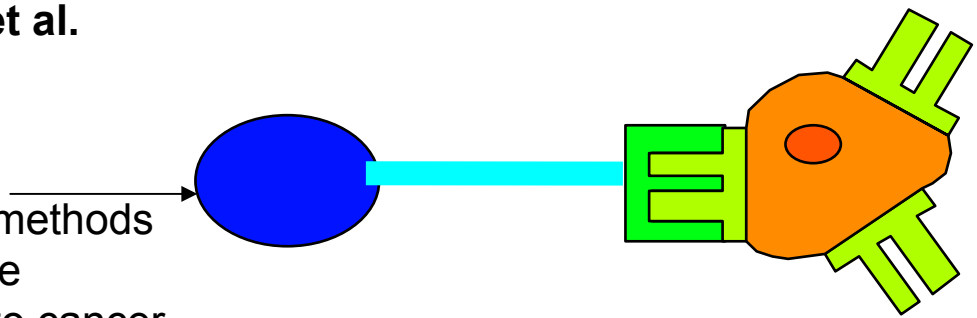


Targeting Chemistry Concept –
Atcher, Berning, et al.

We are focusing on receptors that would be present on a cancer cell but NOT on a healthy cell.

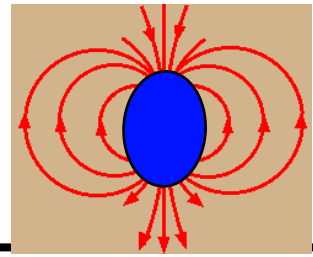
This step is hard!

But people use similar methods for delivering radioactive treatments specifically to cancer



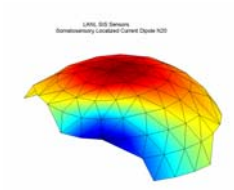
Magnetic particle bound to cell

Carcinotherapy: Image



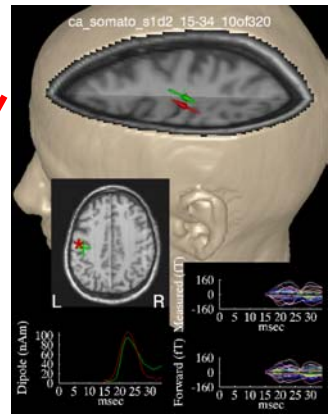
- **Imaging of magnetic particles at tumor can be done with same techniques used in MEG**

Instrumentation



Modeling & Computation

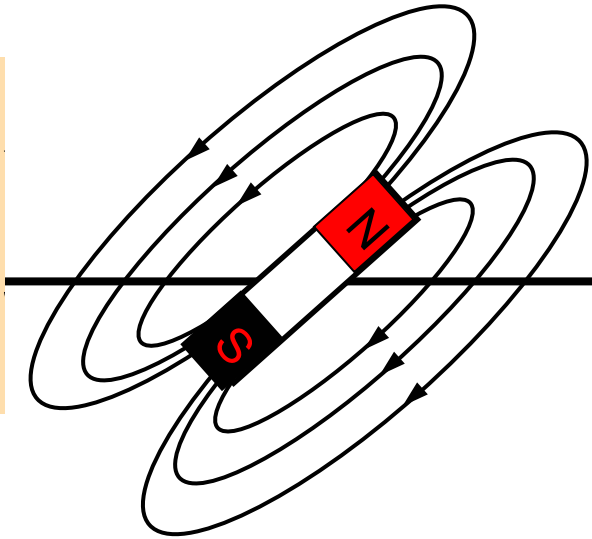
Visualization



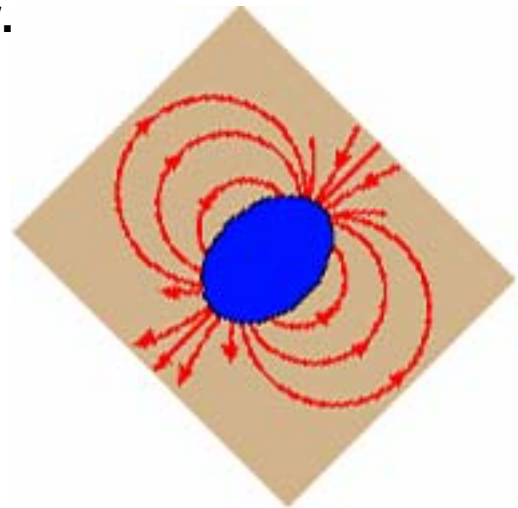
Localizing *concentrations of magnetic particles in vivo uses techniques developed for functional brain mapping*

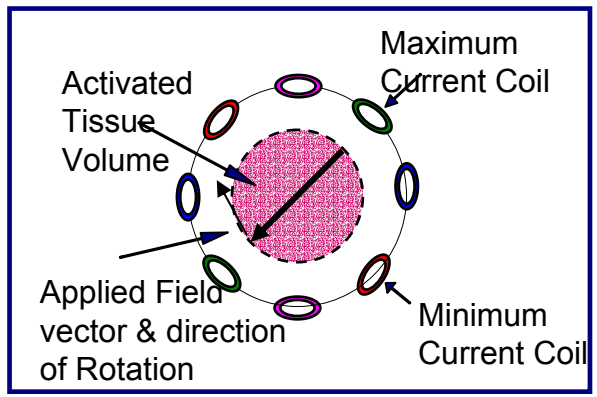
- **To image a tumor of 1/100 to ½ inch in size, 1 inch away, imagining you can deliver 20x more material to the tumor than to healthy tissue, you need ~20 nanograms (about 1/2000 of a grain of salt).**

Carcinotherapy: Treat



- **The needle on a compass wants to line up with a magnetic field.**
- **Similarly, our magnetic particles are like tiny compass needles and will line up in a magnetic field.**
- **If the magnetic field rotates, our magnetic bead will follow it. Acting like a little stirring bar.**

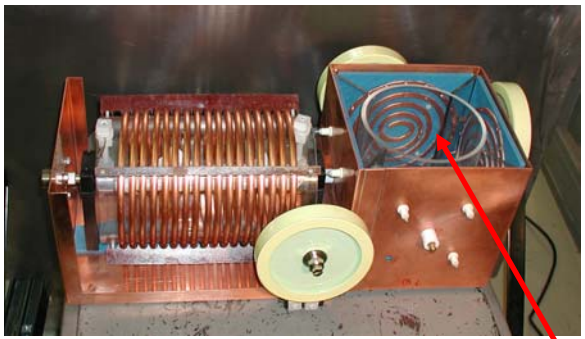




Carcinotherapy: Treat

- **The rotating magnetic heats particles >45 F in <<1min**

- **Tumor is killed with minimal damage to nearby healthy tissue**



Hardware supplied by SNS Division

Put a sample (tissue, salt water, etc.) inside this box and see how the heating progresses in the material with magnetic beads vs. the material without.

Carcinotherapy: Treat

- To treat, one needs ~ 5 micrograms (about 1/10 a grain of salt) in a tumor of size ~1/100 inch.
- So far we are only testing on samples.
- But the idea is that if you were applying this treatment to a person, the tumor would be killed and when the treatment was over the body would eliminate the beads through the kidneys.
- The benefit to this method is that it targets primarily ONLY the cells that are unwanted.

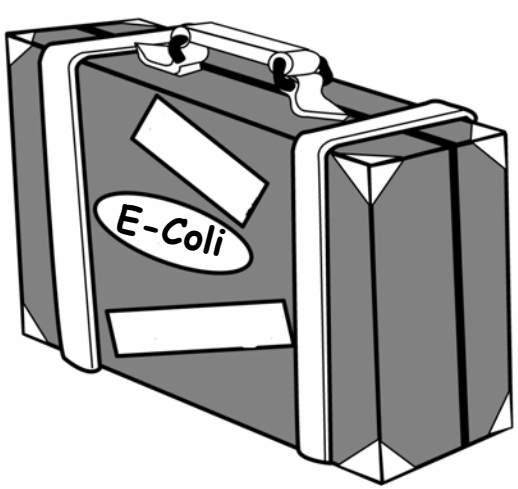
- The idea of heating tissue with magnetic fields to kill cancer is decades old and called Hyperthermia
- Our idea is different because the magnetic material is so strong. But targeting is still being developed!

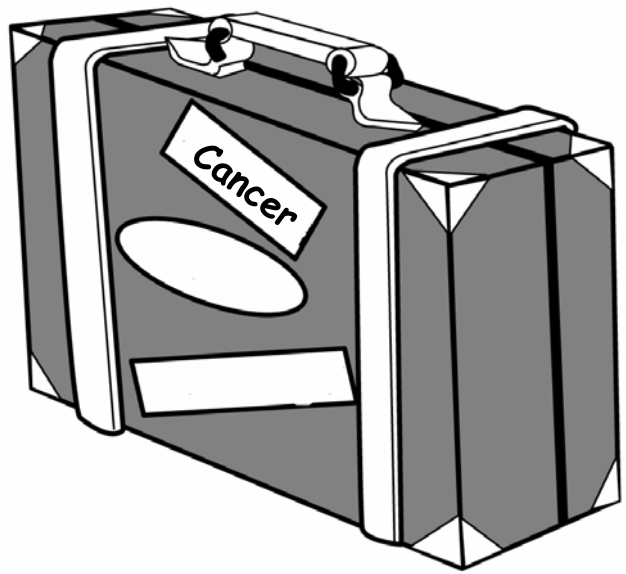
Bioassay: What is it?

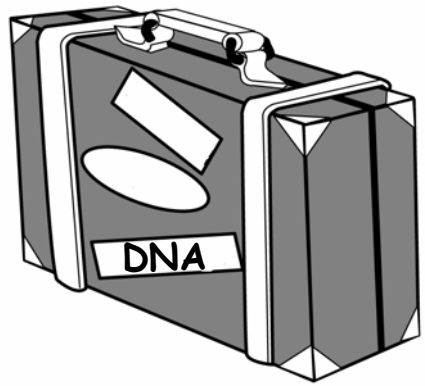
Bioassay is a way of determining the strength or biological activity of a substance. This can be done on a living system or on a sample (tissue, blood, etc.).

For example, lets say you wanted to know if a person had a certain DNA sequence, or a certain virus…

Desire to look for a large number of agents simultaneously







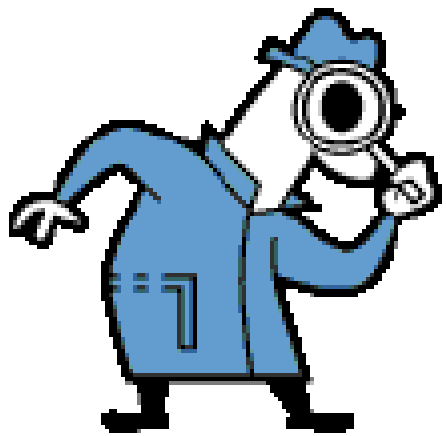
Bioassay: Why?

Imagine you are some sort of bio-detective:

What is in that envelope of white powder?

What strain of flu does the patient have?

Maybe you don't really know what you are looking for and want to match your evidence with many possibilities….

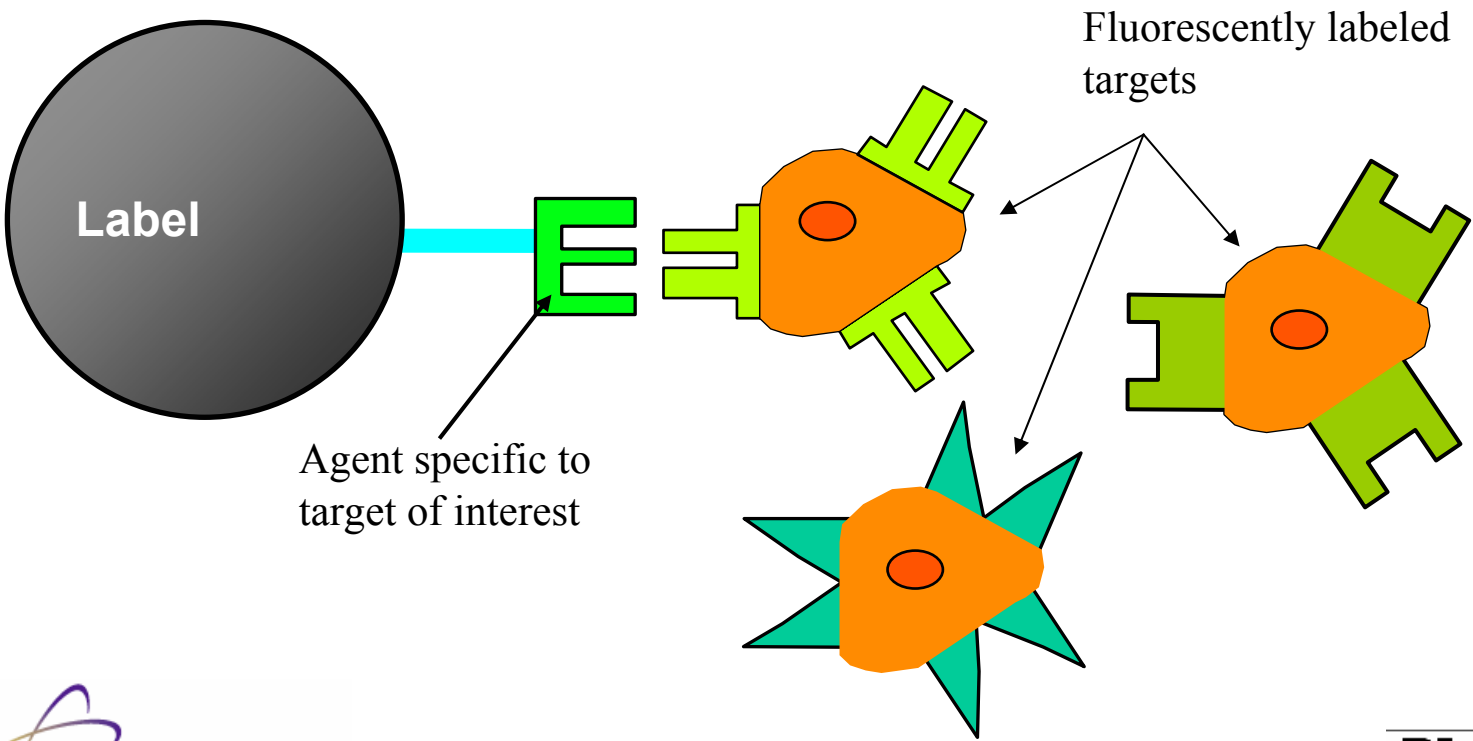


General Approach

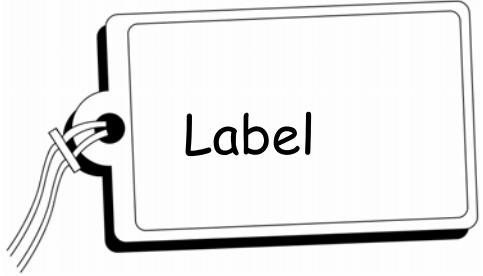
Attach a label to an agent specific for the target

Let the label+agent mix with the sample (agent will bind specifically with the target)- in vitro we do a 100 to 1000 times better than in the body!

Targets are made such that target + tag is fluorescent – shining a laser and looking for the light can tell if you've got a match



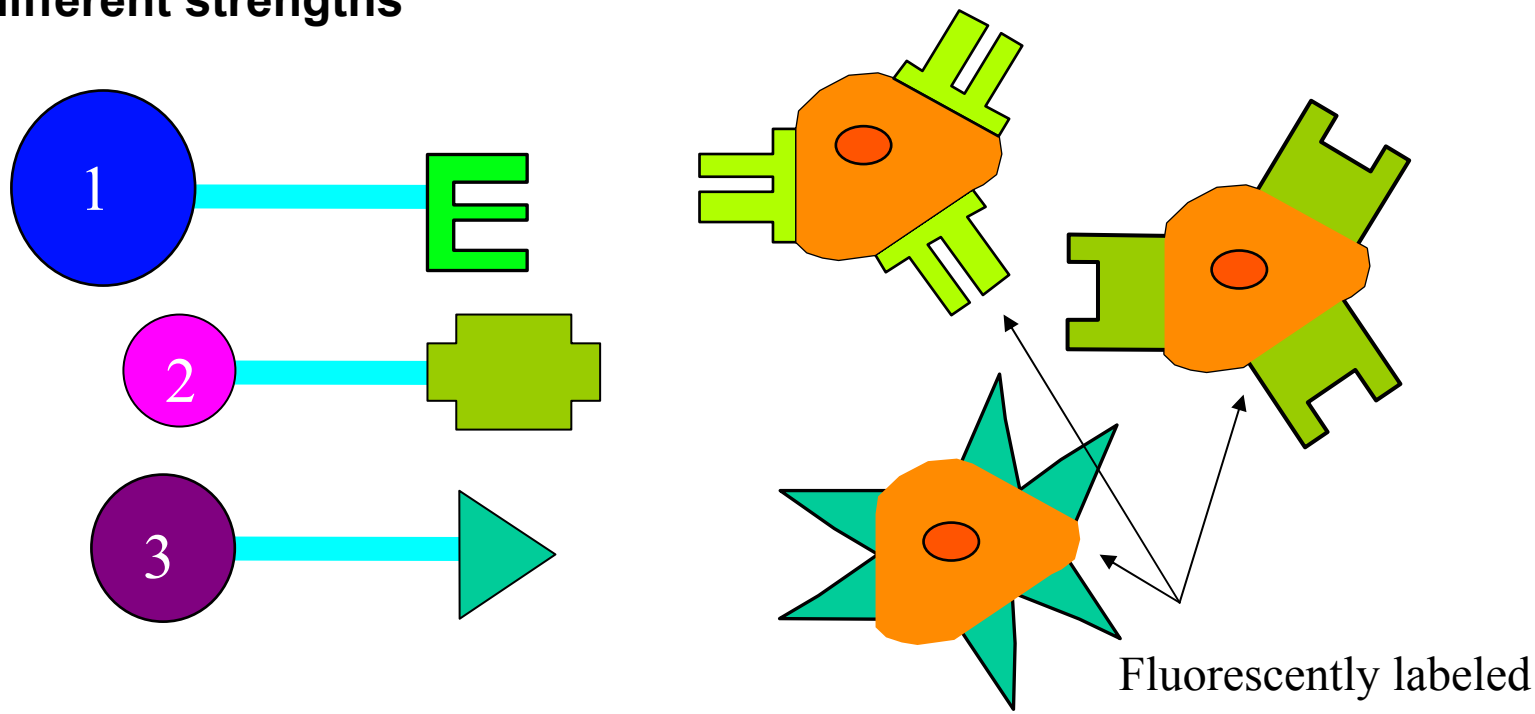
Look for more than one thing



Use different labels:

1) Colored beads with lasers sorting, Flow Cytometry
The National Flow Cytometry Resource is at LANL

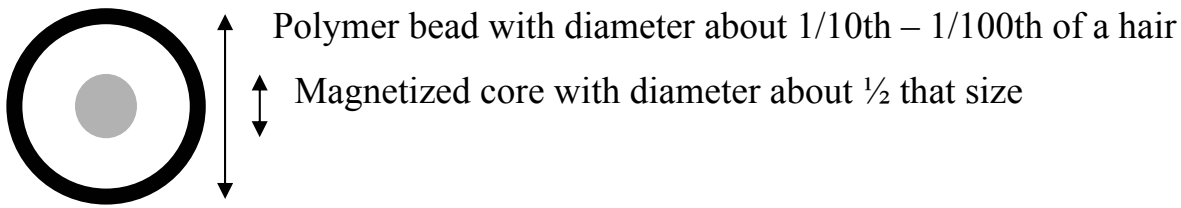
2) Or you could use magnetic beads (little bar magnets) with different strengths



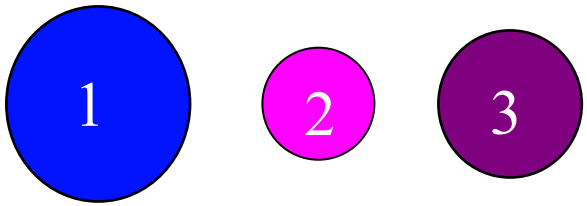
Bioassay with magnetic nanoparticles

What is a magnetic nano-particle?

A magnetic bead that is VERY small, ranging in sizes from the width of human hair to smaller than a bacteria. The beads will have different magnetic strengths (sizes) but are coated so they are roughly the same size on the outside.

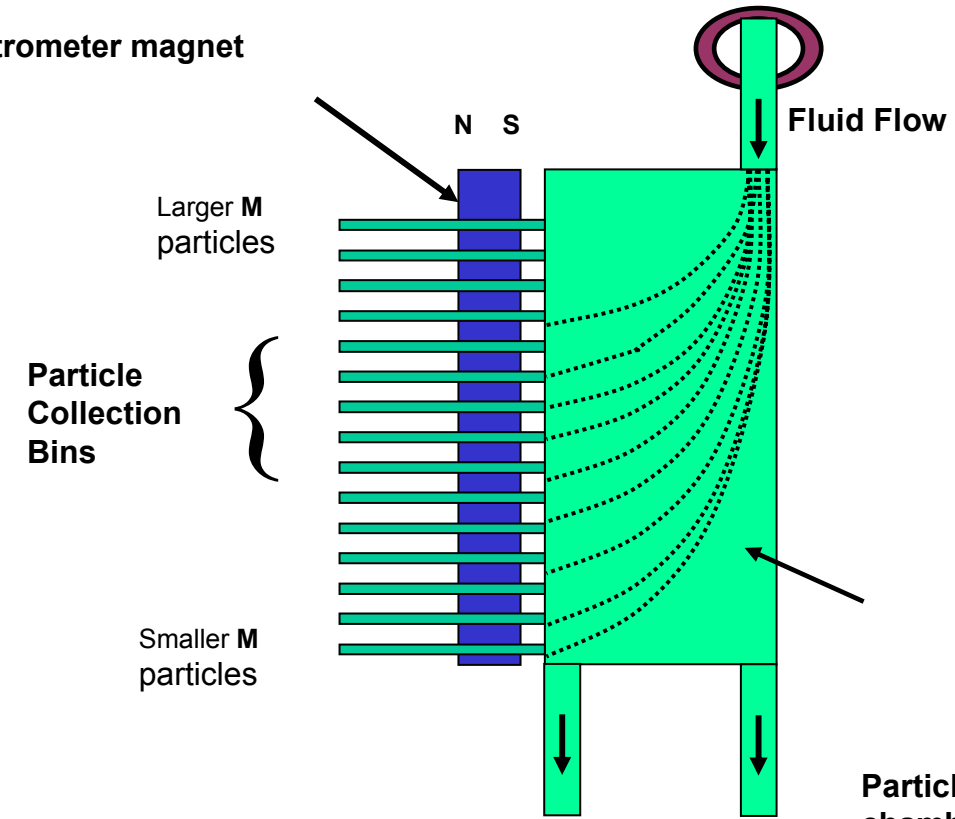


Bioassay with magnetic nanoparticles: First you sort



Pulsed magnets to
activate magnetic particles

Spectrometer magnet



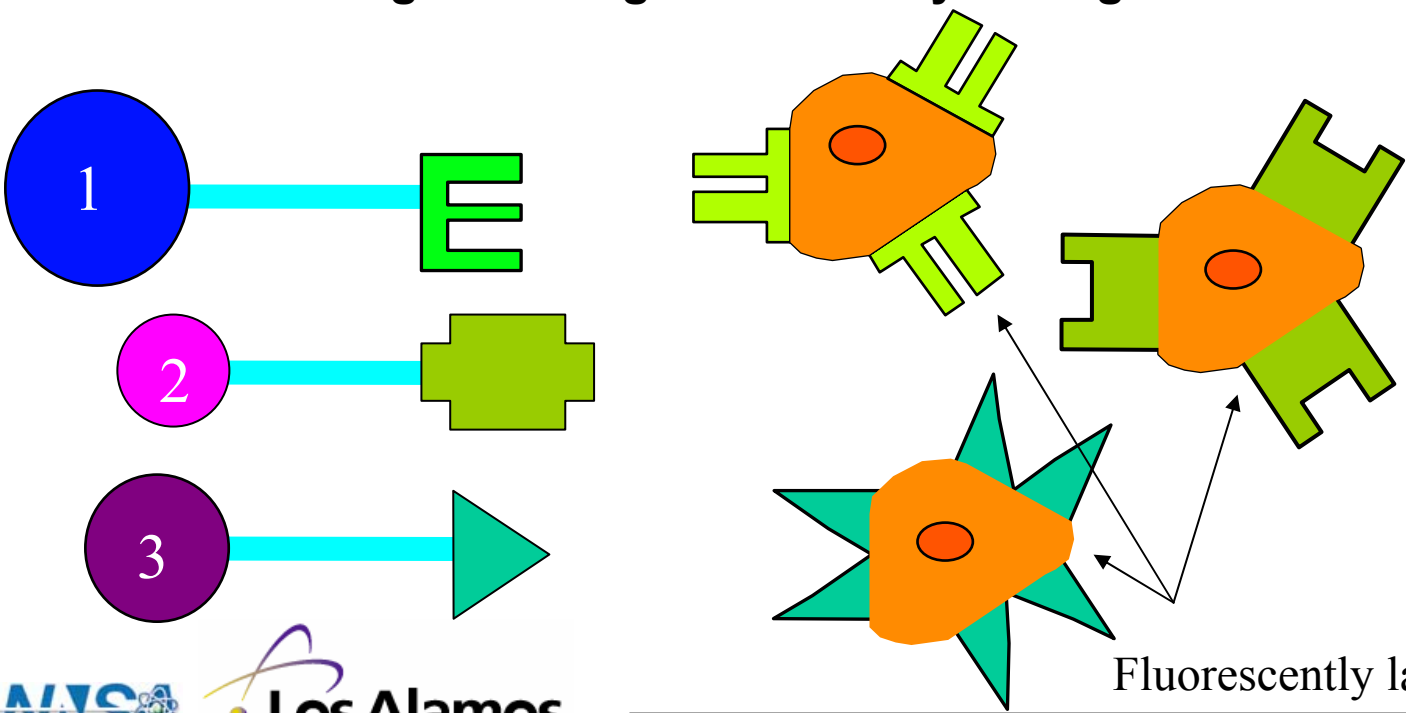
Particle “spectrometer”
chamber

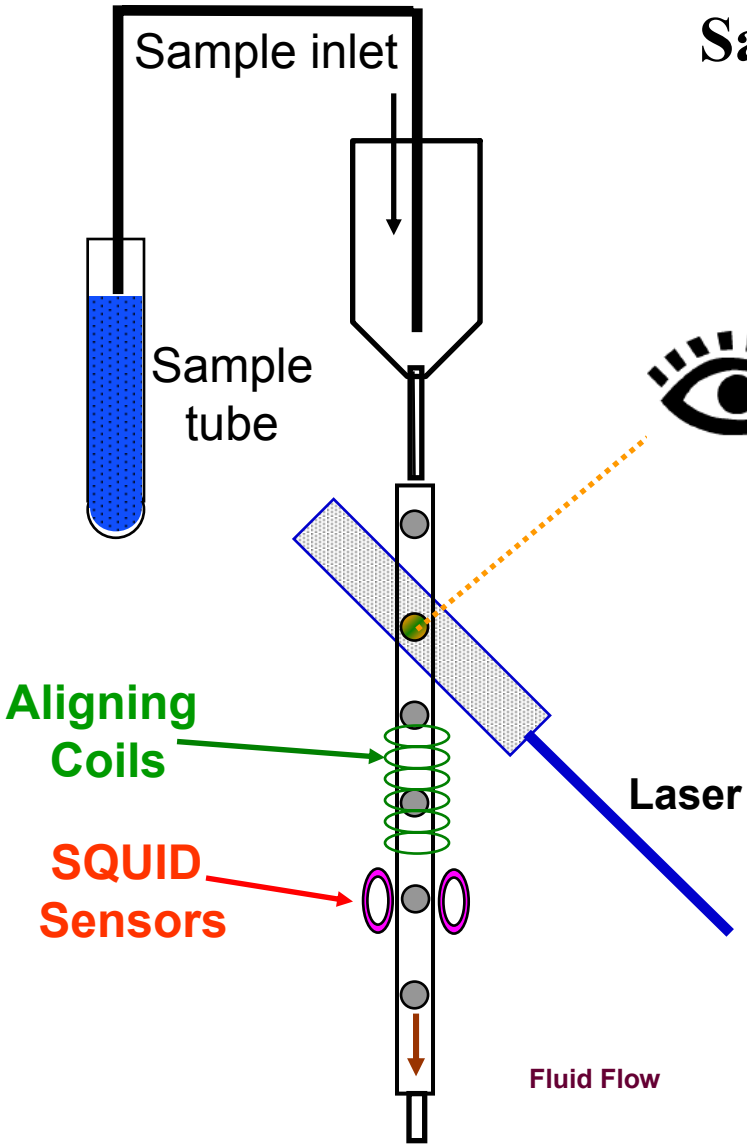
Bioassay with magnetic nanoparticles: Incubate

Attach a label to an agent specific for the target

Let the label+agent mix with the sample

Targets are made such that target + tag is fluorescent – shining a laser and looking for the light can tell if you've got a match



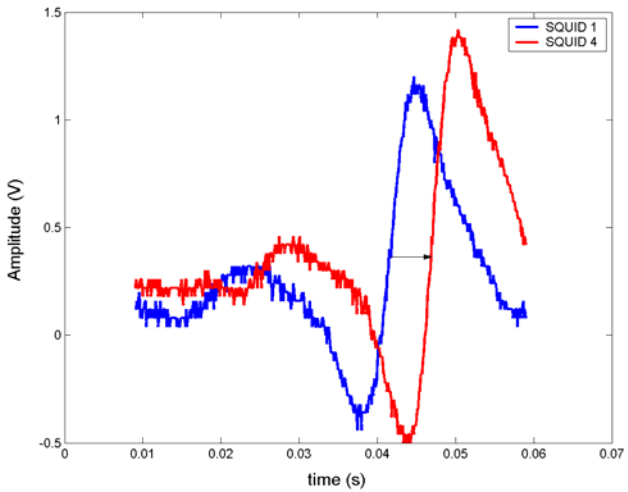


Sample (in tube) introduced in flow

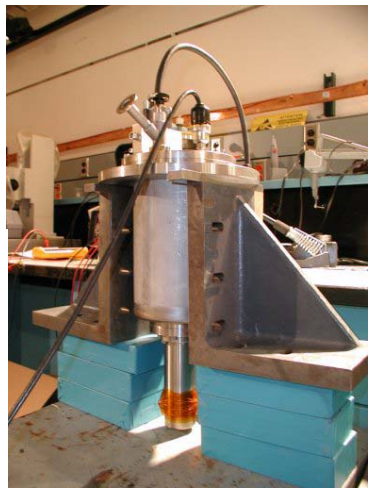
Illuminated by laser, fluorescence tells you there was binding, don't really do this with your eye!

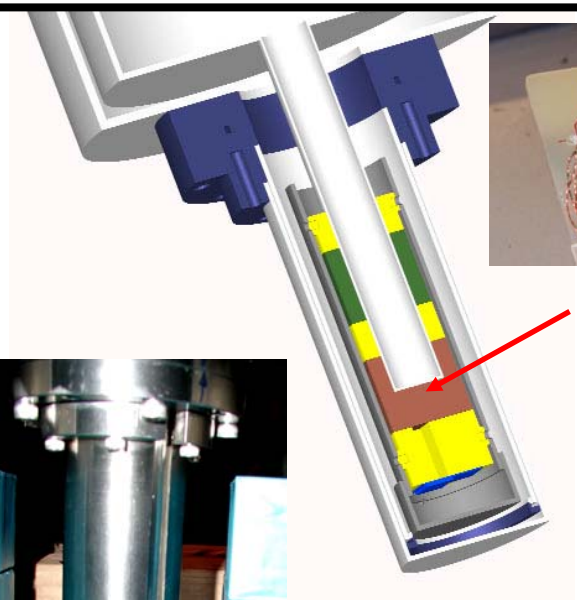
Flows past SQUID to tell you what kind of label

Bioassay with magnetic nanoparticles: present status



Signal from a bead passing under two SQUIDs. By knowing the separation and the timing shift we can calculate that the bead is traveling about 20 inch/sec.





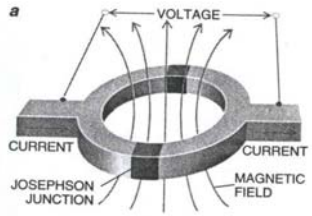
SQUID array

The hardware: thermos with tail section, and a tube that runs through

NNSA Los Alamos

Physics

Concluding remarks

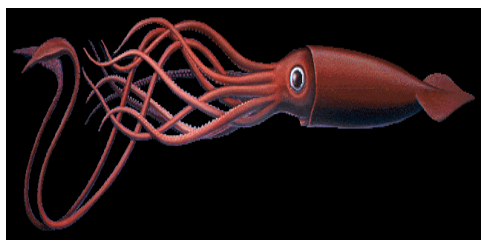


- **SQUIDs are among the world's most sensitive magnetic field detectors.**

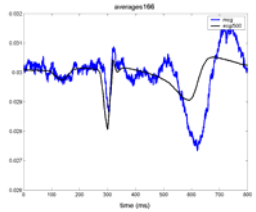
- **The Biophysics group applies SQUIDs to problems in support of the laboratory's mission, from brain imaging to basic physics.**

- **Never use a SQUID unless you have to.** **(Weinstock's Law)**

- **When nothing else will work- try a SQUID!**



Concluding remarks



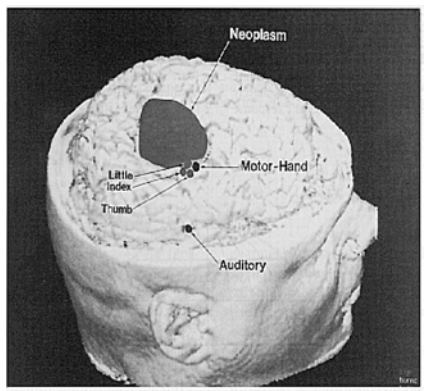
The brain and heart are electric, and thus magnetic.

We use SQUIDs to measure these magnetic signals, to understand how the brain and heart function, when people are healthy or suffering from an illness.

One can also make the processes of interest magnetic and use the sensitivity of SQUIDs to monitor them. This area is new and we are just beginning.

At Los Alamos we are building several systems to measure magnetic fields more effectively.

SQUIDs are the tool, but the goal is to improve the quality of life.



Thank you!